Clinical Handbook of Insomnia

Edited by

Hrayr P. Attarian, MD

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Clinical Handbook of Insomnia

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To my wife Diana with unending love

Series Editor's Introduction

The areas of sleep research as a scientific discipline and sleep medicine as a medical specialty are relatively new but rapidly growing areas of interest. Early investigations in sleep emphasized disorders of excessive daytime sleepiness. However, among the sleep disorders, insomnia may be the most common and yet, at the same time, the least well-managed sleep disorder. To many patients and physicians, insomnia is presumed to be the result of underlying anxiety, recognized or unrecognized. Perhaps for this reason, large numbers of affected individuals do not seek medical attention but self-treat with alcohol or relatively ineffective over-the-counter medications.

As stated in the *Clinical Handbook of Insomnia*, contrary to popular belief, psychological factors are not the most common causes of insomnia and, very appropriately, clues to possible physiologic causes of insomnia are given important attention. On the other hand, the authors in this volume emphasize that untreated insomnia may be an important risk factor for secondary psychiatric morbidity. Surprisingly, it is currently unclear whether insomnia should be considered a disorder of sleep or a disorder of arousal. Insomnia is a symptom, not a disease, but apparently can occur as a primary or secondary disorder. *Clinical Handbook of Insomnia* carefully defines insomnia, emphasizes the broad scope of the problem worldwide, discusses its differential diagnosis, differentiates the primary and secondary insomnias, and reports critically on the available modes of behavioral and pharmacologic treatment.

This collection within a single volume of very practical information concerning a common, but often neglected, disorder will be a useful addition to the armamentarium of the generalist or specialist who wishes to deal with insomnia in an intelligent and responsible manner.

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Foreword

It is a pleasure and honor for me to introduce this most important *Clinical Handbook of Insomnia*, edited by Hrayr Attarian, MD. For too long, the complaint of insomnia has been ignored, trivialized, or summarily (often erroneously) attributed to underlying or pre-existing psychiatric or psychological problems (themselves often ignored or trivialized). This book clearly underscores the fact that insomnia extracts a huge toll—in the form of personal misery, societal financial burden, lost productivity, and strained interpersonal relationships.

One reason the complaint of insomnia is often not pursued by physicians is that the evaluation and management may be time consuming and therefore difficult to execute in the current medical climate. Another is that physicians tend not to want to deal with conditions that are perceived as difficult or discouraging to manage. Many physicians have not had positive reinforcement from predictable success in treating insomnia—their past experience does not anticipate a favorable outcome. *Clinical Handbook of Insomnia* provides a systematic approach to the diagnosis and management of insomnia, which will result in more gratifying doctor–patient encounters—with the patient improving, and the physician being positively reinforced.

As with other constitutional symptoms, such as pain, fever, or weight loss, insomnia is a manifestation of myriad underlying conditions that, appropriately identified, is effectively treatable. The algorithm in Chapter 4 is particularly helpful in this regard.

One important emphasis of *Clinical Handbook of Insomnia* is the growing scientific evidence that much insomnia has biological underpinnings, with many individuals having a genetic or constitutional predisposition to develop insomnia—triggered by environmental events or situations. Once this insomnia has developed, it may become persistent, despite resolution of the initial instigators, and will not spontaneously improve until behavioral and/or pharmacologic treatment is undertaken. This is reason enough for aggressive treatment of acute, situational insomnia—to prevent the development of persistent psychophysiologic, learned, or conditioned insomnia.

Furthermore, it is now clear that insomnia, initially not associated with depression, is a major risk factor for the development of depression—another reason for prompt diagnosis and aggressive treatment.

The encouragement of pharmacologic treatment of insomnia is welcome, inasmuch as there are now many very effective sedative/hypnotic agents available. The tendency has existed to prescribe ineffective or potentially more toxic agents owing to exaggerated and unfounded fears associated with prescribing those agents that are truly effective. Just as physicians are comfortable prescribing long-term stimulants for hypersomnolent conditions such as narcolepsy or idiopathic central

nervous system hypersomnia, they should be comfortable prescribing long-term sedative/hypnotics in hyposomnolent conditions. There has been a failure to distinguish between drug-seeking behavior and therapy-seeking behavior. This fear of drug abuse results in patient abuse.

This is certainly the most extensive insomnia textbook available. Dr. Attarian should be commended for compiling this group of distinguished and experienced authors who provided such thoughtful and excellent contributions. The benefactors will be both patients and treating physicians.

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Preface

Insomnia is the second most common complaint, after pain, in the primary care setting. Persistent insomnia affects roughly more than one-third of the population and is a risk factor for significant psychiatric morbidity.

Insomnia also leads to over-utilization of health care services, decreased productivity in the workplace, more accidents, and more absenteeism from work. All this costs about $100 billion annually. Hence, persistent insomnia is both a public health and an economic problem. Insomnia is not, however, one distinct illness. There are many causes and each naturally requires a different method of evaluation and treatment. Patients with insomnia frequently self-treat with alcohol or over-the-counter medications. There is no scientific evidence for the efficacy of these medications in insomnia. Additionally, those taking these medications may suffer impaired daytime functioning caused by lingering feelings of sedation.

Most medical school curricula suffer a dearth of material on sleep medicine as well as insomnia. Primary care text and reference books often do not include chapters that address the evaluation and treatment of insomnia. The *Clinical Handbook of Insomnia* represents the first clinically oriented, easily readable textbook dedicated to the evaluation and treatment of insomnia in the primary care setting. Our goal is to provide practitioners in general and primary care providers specifically with an easily accessible handbook to serve as a reference for the evaluation and treatment of this important yet poorly recognized medical problem.

The *Clinical Handbook of Insomnia* is divided into four sections. The first discusses definitions, differential diagnosis of insomnia in adults and children, the epidemiology, and the pathophysiology of insomnia. The second section focuses on the primary insomnias. Part III discusses the secondary insomnias or insomnias arising from other medical problems. Part IV reviews the pharmacological and nonpharmacological treatments of insomnia. Most of the chapters are illustrated by case studies, algorithms, and charts and graphs to better elucidate the points conveyed.

We hope the *Clinical Handbook of Insomnia* will fill an important niche in the medical literature by providing the first comprehensive publication that addresses insomnia in its multiple forms, summarizes the findings published in different medical journals, and presents the findings to the practicing health care provider in an easily readable format.

***Hrayr P. Attarian,* MD**

Contents

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I Overview

1

Defining Insomnia

Hrayr P. Attarian, Pallavi Nishith-Davis, Carla R. Jungquist, and Michael L. Perlis

Tired Nature's sweet restorer, balmy sleep!

He, like the world, his ready visit pays

Where fortune smiles; the wretched he forsakes

—Edward Young (1683–1765) "Night Thoughts"

INTRODUCTION

In the early 1980s, as the sleep medicine movement was just gathering steam, there was perhaps no rallying cry as popular as "insomnia is a symptom, not a disorder." Presumably, this position was taken in part for medico-political reasons, but also because it was genuinely believed that the polysomnographic study of sleep was destined to reveal all the underlying pathologies that give rise to the "symptoms" of insomnia—fatigue and sleepiness. After two decades or more of sleep research and sleep medicine, it is interesting to find that "all things old are new again": insomnia is once again considered a distinct nosological entity. Perhaps what is different in the modern era is that the distinction between primary and secondary insomnia allows for difficulty initiating and maintaining sleep to be both a disorder in its own right and a symptom of other disorders.

HISTORICAL PERSPECTIVES

The first references in the Western culture to insomnia, the inability to initiate and or maintain sleep, date back to the ancient Greeks. The earliest mention of insomnia is in the pre-Hippocratic Epidaurian tablets that list 70 cases, one of which is of a patient with insomnia. The first scientific approach is found in the writings of Aristotle from circa 350 BC, and the first records of treatment of insomnia come from the first century BC Greek physician Heraclides of Taras, who lived in Alexandria and recommended opium as the treatment of choice. Although there were significant amounts of research and interest in insomnia in the 20th century, it was not

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until the 1970s that distinct diagnostic criteria were created to describe different forms of the disorder.

Over the years, insomnia has been featured in the writings of several prominent literary figures, including William Shakespeare, who alluded to it in several of his plays, to the pop culture icons the Beatles who referred to it in their song "I'm So Tired." Prominent historical figures who reportedly suffered from insomnia include Winston Churchill, Charles Dickens, Napoleon Bonaparte, Marcel Proust, Alexander Dumas, and Benjamin Franklin.

DEFINITIONS OF INSOMNIA

Insomnia is the most common sleep-related complaint and the second most common overall complaint (after pain) reported in primary care settings *(1)*. It affects 35% of the general population, according to the 1984 report of the National Institutes of Mental Health *(2)*, and is a cause of significant morbidity *(1)*. It costs the American public about $100 billion annually in medical expenses, ramifications of accidents, and reduced productivity due to absenteeism and decreased work efficiency *(3)*.

Insomnia is not defined by total sleep time (TST) but by the inability to obtain sleep of sufficient length or quality to produce refreshment the following morning *(4)*. For example, a person who needs only 4 hours of sleep does not have insomnia if he or she is refreshed in the morning after having 4 hours of sleep, whereas someone who needs 10 hours of sleep may have insomnia if he or she does not feel refreshed even after 8 hours of sleep. Contrary to popular lore, psychiatric or psychological factors are not often causes of insomnia *(1)*. In fact, long-standing insomnia can be a significant risk factor for development of depression and anxiety disorders *(5,6)*.

Classifications

There are three major classification systems used by professionals: *The International Classification of Diseases* (*ICD*) by the World Health Organization (WHO), the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual on Mental Disorders, fourth edition* (*DSM-IV*), and *The International Classification of Sleep Disorders-Revised* (*ICSD-R*) by the American Academy of Sleep Medicine (AASM).

WHO: ICD

The WHO defines insomnia as a problem initiating and/or maintaining sleep or the complaint of nonrestorative sleep that occurs on at least 3 nights a week and is associated with daytime distress or impairment *(7)*.

APA: DSM-IV

The APA defines two types of insomnia, primary and secondary.

The term *primary insomnia*, which is adopted by the APA's diagnostic nomenclature, *DSM-IV (8)*, is used to distinguish insomnia that is considered to be a dis-

Table 1
Diagnostic Criteria for Primary Insomnia

A. Difficulty initiating or maintaining sleep for at least 1 month.
B. The disrupted sleep and the associated daytime fatigue causes clinically significant distress and impaired functioning.
C. The sleep disturbance cannot be attributed to any other sleep disorder.
D. The sleep disturbance cannot be attributed to any other psychiatric disorder.
E. The sleep disturbance cannot be attributed to any other medical disorder or substance abuse.

Adapted from ref. *8*.

tinct diagnostic entity from insomnia that is a secondary symptom of an underlying medical and/or psychiatric condition. The APA specifies a duration criteria of 1 month and stipulates that the diagnosis be made when the predominant complaint is difficulty initiating or maintaining sleep or nonrestorative sleep. In either case, the complaint must be associated with significant distress and daytime impairment, and not due to other medical, psychiatric, or sleep disorders. Table 1 lists the diagnostic criteria for primary insomnia.

AASM: ICSD-R

AASM's nosology, the *ICSD-R*, does not have a distinct category of primary insomnia but instead discusses three free-standing insomnia disorders: psychophysiological insomnia, idiopathic insomnia, and sleep state misperception *(9)*.

Psychophysiological Insomnia

The *ICSD-R* definition of psychophysiological insomnia is directly tied to the etiologic underpinnings of the disorder. Psychophysiological insomnia is described as "a disorder of somatized tension and learned sleep-preventing associations that results in a complaint of insomnia and associated decreased functioning during wakefulness" *(9)*. "Somatized tension" refers to either the patient's subjective sense of, or objective measures of, somatic hyperarousal while attempting to sleep. Somatic arousal is characterized by peripheral nervous system activity that is commonly marked by increased muscle tension, rapid heart rate, sweating, and so on. "Learned sleep-preventing associations" refers to the pattern of pre-sleep arousal that appears to be classically conditioned to the bedroom environment, where intrusive pre-sleep cognitions, racing thoughts, and rumination are often taken as indicators of pre-sleep arousal. Table 2 presents the diagnostic criteria for psychophysiological insomnia.

Idiopathic, or Childhood-Onset, Insomnia

This condition presents as a chronic, serious inability to initiate and maintain sleep, which can often be traced back to the first few weeks of life *(10)*. Sleep latency (i.e., the time it takes to fall asleep after going to bed) may be very long, and sleep is riddled with awakenings. Daytime features typically include decreased

Table 2
Diagnostic Criteria for Psychophysiological Insomnia

A. Complaint of insomnia together with a complaint of decreased functioning during wakefulness.
B. Learned sleep-preventing associations that include the following:
   1. Trying too hard to sleep
   2. Conditioned arousal to bedroom or sleep-related activities
C. Evidence for somatized tension.
D. On polysomnography there is
   1. Increased sleep latency
   2. Reduced sleep efficiency
   3. An increased number and duration of awakenings,
E. The sleep disturbance cannot be attributed to any other medical disorder.
F. Other sleep disorders can co-exist.
Minimal Criteria: A plus B.

Adapted from ref. *9*.

Table 3
Diagnostic Criteria for Idiopathic Insomnia

A. Complaint of insomnia together with a complaint of decreased functioning during wakefulness.
B. The insomnia is long standing with onset in childhood and sometimes even at birth.
C. Relentless insomnia invariant through periods of both good and bad emotional adaptation.
D. On polysomnography there is
   1. Increased sleep latency
   2. Reduced sleep efficiency
   3. An increased number and duration of awakenings
E. The sleep disturbance cannot be attributed to any other medical disorder.
F. Other sleep disorders can co-exist.
Minimal Criteria: A plus B plus E.

Adapted from ref. *9*.

attention and vigilance, low levels of energy and concentration, and deterioration of mood that is usually described as grim and subdued rather than obviously depressed or anxious.

The presumed underlying neurological abnormality may vary from mild to severe, so the range of insomnia encountered also may vary from mild (essentially, the patient is a light sleeper) to severe and incapacitating. In mild or moderate idiopathic insomnia, psychological functioning is remarkably intact. In severe cases, daytime functioning may be severely disrupted, and the affected patient may be unable to hold a job. During childhood and adolescence, idiopathic insomnia is often associated with such neurological signs as dyslexia and hyperactivity. In many cases, diffuse, nonspecific abnormalities are seen on an electroencephalogram (EEG) *(9)*. Table 3 lists the diagnostic criteria for idiopathic insomnia.

Table 4
Diagnostic Criteria for Sleep State Misperception

A. Complaint of insomnia
B. Normal sleep quality and duration
C. Normal polysomnography
D. The sleep disturbance cannot be attributed to any other medical disorder.
E. Other sleep disorders can co-exist.
Minimal Criteria: A plus B.

Adapted from ref. *9*.

Sleep State Misperception Insomnia

In this fascinating disorder, complaints of insomnia occur without any objective evidence of sleep disturbance. Patients may report that they have not slept at all in weeks, months, or years. However, on objective sleep studies, they sleep several hours per night *(4,11)*. When results of sleep evaluation are presented, patients with sleep state misperception (SSM) may vehemently insist that the studies are in error because they are convinced that they sleep very little, if at all. Table 4 lists the diagnostic criteria for SSM.

Interestingly, none of the nosologies formally embrace the older descriptive clinical characterizations of insomnia in terms of initial, middle, and terminal (late) insomnia. Trouble falling asleep is often referred to as "initial," early, or sleep-onset insomnia. Trouble with frequent or prolonged awakenings is often labeled "middle" or sleep maintenance insomnia. Waking up earlier than desired and being unable to fall back asleep is referred to as "late," "terminal," or early morning awakening insomnia. Waking up feeling unrefreshed is commonly referred to as "nonrestorative" sleep. Patients often report some combination of these descriptions, which is generally referred to as "mixed" insomnia. For the purpose of this chapter, although we consider the *ICD*'s system to provide a more precise definition of the disorder, we use the term *primary insomnia* because it is the most widely embraced in clinical practice in the United States. We adopt the more descriptive terminology when a more specific characterization of the presenting complaint is required.

Classification Based on Duration and Severity

Apart from presenting a specific definition of the disorder/disease entity, there is the need to qualify the duration and severity of the defined illness. Typically, duration is framed dichotomously in terms of acute and chronic stages. Severity can be construed in one of two ways. In one case, standards are set for what constitutes significant deviance from population norms with respect to frequency and intensity of presenting symptoms. In the other case, standards are set by "setting the bar" for "pathologic" at a level that is modal for patients who are help-seeking.

Duration of Illness

Insomnia lasting less than 1 month is generally considered "acute," and is often associated with clearly defined precipitants such as stress, acute pain, or substance abuse. Insomnia is characterized as being chronic when symptoms persist unabated for a duration of at least 1 month, and more typically for durations of time that are 6 months or greater. These cutoffs are relatively arbitrary and correspond to traditional medical definitions of what constitutes short and long periods of time. At this time, there are no studies that use risk models to evaluate the natural course of insomnia. Thus, there is no way of definitively defining "chronicity" in terms that are related to when the disorder becomes severe, persistent, and (for want of a better expression) "self-perpetuating." One clinical cue for differentiating between acute and chronic insomnia resides in the way patients characterize their complaints. When patients stop causally linking their insomnia to its precipitant and instead indicate that their sleep problems seem "to have a life of their own," this change in presentation may serve to define the "cut point" between the acute and chronic phases of the disorder and suggest when cognitive-behavioral therapy should be indicated.

Severity of Illness

Intensity

Although there are no formal diagnostic criteria, most investigators consider 30 or more minutes to fall asleep and/or 30 or more minutes of wakefulness after sleep onset to represent the threshold between normal and abnormal sleep. Recent work by Lichstein and colleagues suggests that this criteria should be set at "more than 30 minutes," as this definition is better related to the occurrence of complaint in population studies *(12)*. With respect to "how much sleep," many investigators are reluctant to fix a value for this parameter. Of the investigators who are inclined to set minimums, most specify that the amount of sleep obtained on a regular basis be equal to or less than either 6 or 6.5 hours per night. The reluctance to establish TST parameters is due, in part, to the difficulty in establishing precisely what one considers to be abnormal. Representing what is pathological with a single number is too confounded by factors like age, prior sleep, and the individual's basal level of sleep need. The lack of an established TST cutoff is also related to the possibility that profound sleep initiation or maintenance problems may occur in the absence of sleep loss. This is an important distinction because it is often assumed that insomnia is synonymous with sleep deprivation. Although it is certainly the case that the daytime symptoms associated with insomnia might be explained, in part, by partial chronic sleep loss, daytime symptoms need not be ascribable only to lack of sleep. For example, it has been shown that patients with insomnia reliably exhibit sleep micro-architectural disturbances such as enhanced high-frequency activity during non-rapid eye movement (NREM) sleep *(13–17)*. This type of activity, which appears to be independent from sleep continuity and architecture parameters, has been shown to be correlated with patient perceptions about sleep quality and quantity *(13,18,19)*.

FREQUENCY

There is also no fixed benchmark for "frequency" of symptoms. Most clinical researchers, in this case, require that subjects experience problems on at least 3 nights per week, but this may have more to do with increasing the odds of studying the occurrence of the disorder in laboratory than an inherent belief that less than 3 nights per week is "normal."

Commonalities and Problems with Current Definitions

All of the definitions just given show a degree of consistency, both in terms of what "is" and "is not" delineated. Common to all is that (1) insomnia is defined as a subjective complaint, (2) patients must report compromised daytime functioning, (3) there are no specific criteria for how much wakefulness is considered pathologic (prior to desired sleep onset or during the night), and (4) there are no criteria for how little total sleep must be obtained to fall outside the normal range. The latter two of these issues have already been explicated (lack of quantitative criteria for sleep latency, waking after sleep onset, and TST). The former two require further discussion.

Insomnia as a Subjective Complaint

Defining insomnia as a subjective complaint without requiring objective verification of signs and symptoms has advantages and disadvantages. The advantage of having subjective criteria is that it recognizes the primacy of the patient's experience of distress or disease. That is, ultimately patients seek, comply with, and discontinue treatment based on their perception of wellness. The disadvantage is that such measures, when used alone, do not allow for a complete characterization of either the patient's condition or the disorder in general.

Insomnia and Daytime Impairment

The reason that daytime complaints are required for diagnosis is that in the absence of such complaints, it is possible that the phenomena of "short sleep" may be misidentified as insomnia. Frequent complaints associated with insomnia include fatigue, irritability, problems with attention and concentration, and distress directly related to the inability to initiate and/or maintain sleep.

SUMMARY

We are fortunate to have several nosologies that recognize insomnia as a primary disorder. The various classification systems provide the wherewithal to differentiate types of insomnia both by presenting complaints as well as by the factors that are thought to precipitate or perpetuate the illness. Perhaps what remains to be accomplished in the present decade, from a definitional point of view, is for scholars and scientists to complete the characterization of this important disorder by providing for the formulation of the ultimate definition, one that formally lays out the research diagnostic criteria and does so based on the force of empirical research.

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2
Epidemiology of Insomnia

Hrayr P. Attarian

Insomnia is the most common sleep-related complaint and the second most common overall complaint (after pain) reported in primary care settings *(1)*.

In 1979, in the United States, a survey conducted in a nationally representative sample of 3161 people ages 18–79, found that insomnia affected 35% of the general adult population in 1 year *(2)*. About 50% of these people experienced the problem as severe *(2)*. Only 15% were treated with any sort of hypnotic medications *(2)*. In 1996, another study by Ohayon in Montreal, looked at the prevalence of insomnia in a representative sample (n = 5622) of the French population in subjects of 15 years of age or older. Of the people who participated in the survey, 20.1% said that they were unsatisfied with their sleep or were taking medication to alleviate sleep difficulties *(3)*. The prevalence of frequent insomnia was 29% in a representative sample of the French population that included 12,778 individuals *(4)*. Of the English-Canadian population age 15 or older, 24% reported insomnia as well, according to a 2001 study by Sutton et al. *(5)*. In a representative selection of German citizens older than 13 years of age, 1997 were asked about their sleep complaints. Of this group, 25% reported suffering at least sometimes from difficulties in falling and/or staying asleep, which was not due to external factors, and 7% frequently or always had problems *(6)*. A similar survey in Japan, conducted in a group of 6277 new outpatients from 11 hospitals, revealed a prevalence of 20.3% with insomnia, with 11.7% of the people suffering from it for more than 1 month. Only 37% were treated with hypnotics *(7)*. A second study done in a representative sample (n = 3030) of the general population reported almost identical results: 21.4% during the month preceding the survey *(8)*. A representative adult sample (18 years and older) of the Norwegian population, comprising 2001 subjects, participated in telephone interviews, focusing on the 1-month point prevalence of insomnia and use of prescribed hypnotics. Employment of *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (*DSM-IV*) inclusion criteria of insomnia yielded a prevalence rate of 11.7% *(9)*. A prior study had queried 14,667 subjects and reported 41.7% of the women and 29.9% of the men complaining of occasional insomnia *(10)*.

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Another study in Austria, in a sample of 1000 individuals, revealed a prevalence of 26% with 21% of insomnia symptoms being severe and chronic with a duration of 1 year or more *(11)*. In a representative sample of the South Korean general population composed of 3719 noninstitutionalized individuals aged 15 years or older, the prevalence of insomnia symptoms occurring at least 3 nights per week was reported to be 17% *(12)*. In Mexico, the prevalence of insomnia in a group of 1000 subjects ages 18–84, was found to be 36%, with 16% reporting severe insomnia *(13)*. A host of other studies have shown similar prevalence in various groups of adult subjects: in Finland, an early study reported a severe insomnia (daily of several times a week) prevalence of 5–14%, depending on age group, in subjects between ages 15 and 64. In Singapore, the prevalence of persistent insomnia for more than 1 year was 15.3% in subjects between ages 15 and 55 *(14)*. Hyyppa and Kronholm reported a prevalence of 9.6–12.8% (male/female) of frequent or nightly insomnia and 57.6–62.7% of occasional insomnia in a group of 1099 subjects representative of the Finnish population *(15)*.

There are fewer studies in the pediatric population, but they show a similar prevalence. One of the earliest studies in preadolescent children showed that 14% of an outpatient pediatric population between the ages of 6 and 12 had insomnia with a mean duration of 5 years *(16)*. Archbold et al. at Ann Arbor, surveyed parents of 1038 unselected children (554 boys) aged 2 to 13.9 years. Of these children, 40% had at least one symptom of insomnia and 18% had two or more symptoms *(17)*. The prevalence of frequent insomnia in 1413 school children aged 6.2–10.9 years, in Sweden, was reported to be 13% *(18)*. In adolescent groups, insomnia prevalence is similar to that of younger children and slightly lower than in adults. In a Chinese study, 1365 adolescents between the ages of 12 and 18 years were surveyed and 16.9% reported insomnia *(19)*. A representative sample of 1125 adolescents aged 15–18 years, from four countries—France, Great Britain, Germany, and Italy—revealed insomnia symptoms in approximately 25% and *DSM-IV* insomnia disorder in approximately 4% *(20)*. This confirms previously reported prevalence rates of 4–5% of persistent insomnia in a group of 574 (ages 7–17) *(21)*, 10.8–33.2% of frequent insomnia (at least twice a week) in a group of 40,202 children aged 11–16 *(22)*, and several others that reported rates of 11–12.6% frequent insomnia *(23–25)*, occasional insomnia of 23–38%, and persistent insomnia of 1–2% *(26)*.

In summary, various studies from different countries all show a similar prevalence of insomnia. This confirms that the complaint of insomnia is prevalent universally and constitutes a major health issue.

RISK FACTORS

In a landmark study, Klink et al. identified major risk factors in developing insomnia. They surveyed a large general adult population from 1984 to 1985. They evaluated the relationship among current complaints of initiating and maintaining sleep and obesity, snoring, concomitant health problems, socioeconomic status

(SES), and documented complaints of difficulty with insomnia 10 to 12 years previously. The strongest risk factor for complaints of initiating and maintaining sleep was previous complaints of insomnia (odds ratio [OR], 3.5). Additionally, female gender (OR, 1.5), advancing age (OR, 1.3), snoring (OR, 1.3), and multiple types of concomitant health problems (OR, 1.1–1.7) were all risk factors associated with an increased rate of complaints of initiating and maintaining sleep. They concluded that the complaints of insomnia tend to be a persistent or recurrent problem over long periods of time. Female gender, advancing age, and concomitant health problems also are important risk factors *(27)*. These results have been confirmed by other investigators. Individual risk factors are discussed here.

Gender Predilection

All of the epidemiological studies in the medical literature that compare the prevalence of insomnia between the genders report a higher prevalence in women *(3)*. The female to male ratio is roughly 1.5:1 *(27)*. This is especially true when comparing peri- or postmenopausal women to age-matched men. One of the most common peri-menopausal symptoms in women ranging in age from 35 to 55 is insomnia *(28,29)*.

There are, however, other studies that report increased prevalence in younger women and even in adolescent girls when compared to age-matched male counterparts. When studying a group of children and adolescents between the ages of 3 and 14 (n = 452), Camhi et al. found that the complaints of insomnia were much higher in adolescent girls (ages 11–14) than in the rest of the group (30.4 to 16.8%) *(30)*. This suggests that the increased prevalence of insomnia seen in adult women may begin in early adolescence. The increased prevalence of insomnia in adult women of all ages when compared to men seems to be a universal phenomenon. Studies from Hong Kong *(31,32)*, Germany *(33)*, Canada *(3,5)*, the United States *(2,34)*, Norway *(10)*, Scotland *(35)*, and other countries *(36,37)* have all reported increased prevalence in adult women when compared to age-matched male counterparts.

Ethnocultural Differences in Sleep Complaints

There are only a few studies that look at ethnocultural variables in terms of their effect on insomnia. Most of these studies have shown that, especially in the elderly, Euro-Americans had more complaints of insomnia than African Americans *(38,39)*. In one of the most recent studies, volunteers (n =1118) from a group of older Euro-Americans and African Americans residing in Brooklyn, New York were interviewed. Worse sleep and greater reliance on sleep medicine were observed among the Euro-Americans. Caribbean Americans reported less sleep complaints than did US-born African Americans, and immigrant Euro-Americans reported greater complaints than did US-born Euro-Americans *(39)*. When comparing Euro-American elderly men with Japanese Americans of the same age group, geographic location, and SES, there was no significant difference in reported prevalence of about 30% *(40)*. The impact of ethnicity on the prevalence of insomnia in younger people is

even less well studied. One survey reported the following results among adolescents. Compared with Euro-American youths, Chinese American youths were at significantly lower risk for insomnia, whereas Mexican American youths had an elevated risk, adjusting for the effects of age, gender, and SES *(41)*.

Age and Its Impact on the Prevalence of Insomnia

Advancing age is thought to be a risk factor for developing insomnia. The odds ratio is 1.3 *(27)*. The prevalence of insomnia does increase with age and although several studies from different countries have reported this increased prevalence *(8,9)*, there are in the medical literature a number of studies, especially ones targeting the elderly population exclusively, that have failed to show this effect of aging on the prevalence of insomnia *(36,42,43)*. In 2001, Ohayon et al. surveyed 13,057 subjects age 15 and older from three different countries (United Kingdom, Germany, and Italy). Insomnia symptoms were reported by more than one-third of the population age 65 and older. Multivariate models showed that age was not a predictive factor of insomnia symptoms when controlling for activity status and social life satisfaction. Ohayon et al. concluded that the aging process *per se* is not responsible for the increase of insomnia often reported in older people. Instead, inactivity, dissatisfaction with social life, and the presence of organic diseases and mental disorders were the best predictors of insomnia, age being insignificant. Healthy older people had a prevalence of insomnia symptoms similar to that observed in younger people *(44)*.

Other Factors Impacting Insomnia

Seasonal differences have been reported in patients with chronic insomnia. In Norway, a survey done among a representative sample of 14,667 adults living in the municipality of Tromso, north of the Arctic Circle, revealed increased incidence of complaints of insomnia during the dark period of the year than during any other time *(10)*. Occupation, SES, marital status, and mental and physical health also impact the prevalence of insomnia.

In Finland, in 1984, complaints of insomnia were inquired about in a questionnaire survey of 6268 persons (2801 men; 3467 women, mean age 50.5 years, range 45–57 years) in 40 different occupational groups. Sleep-onset insomnia was highest among bus drivers (18.9%) followed by female cleaners (18.8%) and male teachers (18%). Disturbed nocturnal sleep was highest among male laborers (28.1% waking up at least three times a night), female cleaners (26.6%), and female hospital aides (26.4%). Early morning awakenings were most common among female laborers (13.2% often or always), male construction workers (9.1%), and female cleaners (8.4%) *(45)*. Another survey conducted among Japanese male factory workers revealed that different types of work-related psychosocial stressors were associated with different types of insomnia (sleep onset, sleep maintenance, or terminal insomnia) *(46)*. There was a definite correlation between over involvement at the job and reports of insomnia *(47)*. In a group of US female construction workers, per-

ceptions of having to overcompensate at work and job uncertainty were positively associated with self-reports of insomnia *(48)*. Shift work can naturally lead to complaints of insomnia and several studies have demonstrated that people working on rotating daytime shifts report sleep-onset insomnia more frequently than the fixed daytime schedule workers (20.1% vs 12%) *(49)*. The more shifts one works, the higher the incidence of insomnia complaints. Insomnia and other sleep complaints are significantly more common in three-shift workers than in two-shift workers. By the same token, two-shift workers complain more of insomnia than do straight day-shift workers *(50)*. Also, working the night or third shift, when engaged in for a significant amount of time, may not only acutely cause insomnia but may have persistent deleterious effect on sleep quality even after the individual has reverted to the working day or evening shift *(51)*.

A few studies have reported a direct correlation between being unemployed *(3,8,32,52)* or having a lower SES *(27,32)* or a lower education level *(32)* and increased prevalence of insomnia. Higher prevalence of complaints of insomnia has also been reported among single, widowed, or divorced adults as compared to ones who were in a marital relationship *(3,7,43,52)*. Noisy environments are associated with increased reports of poor sleep particularly in women *(32,53)*. Psychosocial stressors appear to be a risk factor for insomnia as well *(19)*. Poor physical health is also associated with a higher prevalence of insomnia *(7,19,27,31,37,42,43)* as is poor mental health *(7,37,42,43)*. Medical problems associated with insomnia include depressive disorders *(42,54)*, anxiety disorders *(54,55)*, substance abuse *(55)*, schizophrenia *(54)*, congestive heart failure, obstructive airway disease and other respiratory illnesses *(56)*, back and hip problems, and prostate problems *(57)*.

MORBIDITY AND MORTALITY OF INSOMNIA

In 1989, Ford and Kamerow questioned 7954 subjects at baseline and 1 year later using standardized questionnaires. Of this community, 10.2% had insomnia at baseline. The risk of developing new major depression was much higher in those who had insomnia at both interviews compared with those without insomnia. The risk of developing new major depression was much less for those who had insomnia that had resolved by the second visit *(58)*.

In 1997, Chang et al. published a landmark paper on the subject of insomnia and its relation to the development of depression. A total of 1053 men provided information on sleep habits during medical school at The Johns Hopkins University (classes of 1948–1964) and were followed after graduation. During a median followup period of 34 years (range 1–45), 101 men developed clinical depression (12.2%). Of those, 13 committed suicide. In Cox proportional hazards analysis adjusted for age at graduation, class year, parental history of clinical depression, coffee drinking, and measures of temperament, the relative risk of clinical depression was greater in those who reported insomnia in medical school *(59)*.

In the same year, Weissman et al. published a paper that reported data from an epidemiologic community survey of more than 10,000 adults living in three US

communities. A structured diagnostic assessment of psychiatric disorders as well as assessment of the presence of insomnia not due to medical conditions, medication, drug, or alcohol abuse, and a 1-year followup were completed. The results revealed that 8% of subjects with primary insomnia had sought psychiatric help at the end of that year for different psychiatric problems vs 2.5% of the normal controls. Uncomplicated or primary insomnia was also associated with an increase in risk for first onset of major depression, panic disorder, and alcohol abuse over the following year *(54)*. Other studies have confirmed these findings that insomnia is a risk factor for the development of major depression *(60)*.

Other disorders associated with untreated insomnia include alcohol abuse and relapse into alcoholism *(61,62)*, panic disorder *(54)*, and possible coronary artery disease (in men) *(63)*.

Insomnia *per se*, however, is not a cause of increased mortality *(60,64)*. Kripke et al. surveyed and followed 1.1 million subjects for 6 years. Insomnia alone was not associated with increased mortality. There was a suggestion that 8 or more hours of sleep and sleeping pill use is associated with a slight increase in mortality but no causality was determined *(65)*. There is new evidence, however, that there is an association between difficulties falling asleep and mortality due to coronary artery disease in men *(63)*.

There are a number of studies that have demonstrated decreased quality of life as a direct result of the insomnia. Chevalier and colleagues, using SF-36 scores demonstrated the degree of impairment in quality of life was directly related to the severity of insomnia. They also demonstrated that individuals with severe insomnia showed a higher level of health care consumption *(36)*. Hajak and the Study of Insomnia in Europe group in Germany and Leger and colleagues in France reported very similar results regarding quality of life and health care consumption *(33,66)*. Zammit et al. and Hatoum et al., independently, reported similar results in the United States *(67,68)*. Cognitive deficits identified on objective testing have been associated with chronic persistent insomnia as well *(69,70)*.

EPIDEMIOLOGY OF HYPNOTIC USE

The use of hypnotics has been generally low among people reporting insomnia. In the landmark study in the United States in 1979, Mellinger reported the use of any kind of hypnotic medication to be only 15% and only 2.6% of insomniacs used prescribed hypnotics *(2)*. In 1998, Johnson et al. reported similar numbers; 18% were using hypnotic medication, suggesting that there has not been a significant change in the use of hypnotics over a period of 11 years *(71)*. Other countries report similar statistics in the use of hypnotics. Lopez et al. reported that only 10.5% of insomniacs in Mexico used hypnotic medication *(13)*. Sweden *(72)*, Finland *(15)*, Great Britain *(73)*, Australia *(74)*, and France *(3,75)* reported similar numbers. Use of hypnotics increases with age, particularly among middle-aged and elderly women *(75,76)*. Sleeping pill use varies with the person's occupation also. According to one study, male gardeners, female social office workers, and male construction

workers tended to be frequent or habitual users of hypnotic medications more than other surveyed occupations *(45)*. Alcohol, unfortunately, is the most commonly used hypnotic among insomniacs (roughly 15% have reported using alcohol in an attempt to self-medicate) *(55,71)*. The underutilization of proper hypnotic medication is also seen among health care providers treating patients with insomnia. From 1987 to 1996, there was a dramatic shift in the United States toward the use of antidepressants in lieu of hypnotics for the symptomatic treatment of insomnia despite a paucity of data regarding their efficacy and the potential for serious side effects *(77)*. Antidepressants and over-the-counter sleep aids remain the most commonly recommended and prescribed treatments for insomnia complaints *(77)*.

Statistics available from Scandinavia (Finland, Norway, and Sweden) suggest that benzodiazepines and nonbenzodiazepine hypnotics (zopiclone, zolpidem, and zaleplon), particularly zopiclone, are the hypnotics of choice in those countries *(78)*.

ECONOMIC IMPACT OF INSOMNIA

Insomnia costs the US public $92.5 to $107.5 billion annually, in both direct and indirect expenses including medical expenses, ramifications of accidents, and reduced productivity due to absenteeism and decreased work efficiency *(79)*. In France, it has a similar financial impact. According to a recent study, its direct annual cost (i.e., medical expenses including medications and health care), in 1995, was FF 10,232,992,500 ($2,067,271,100 US) *(80)*. In the same year, Walsh and Engelhardt reported a total direct cost of $13.9 billion in the United States *(81)*.

CONCLUSION

Insomnia is a prevalent complaint in the health care field. It is costly and can cause significant morbidity if not addressed appropriately. Women and the elderly tend to suffer from insomnia more than other groups of the population. Other risk factors include psychosocial stressors, psychiatric and medical problems, low income, unemployment, excessive environmental noise, not having a life partner, job-related stressors, and so on.

Patients with insomnia are undertreated and hypnotics are significantly underutilized. Alcohol, unfortunately, remains the most commonly preferred method of self-treatment for insomnia.

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3

Physiological Basis of Insomnia

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INTRODUCTION

Patients with insomnia often have symptoms that include tension, anxiety, depression, fatigue, and irritability (1–4). Frequently, insomnia begins in conjunction with significant stress *(5)*. As a result, many investigators hypothesized that insomnia is the result of internalization of emotions producing emotional arousal. More recently, it has been hypothesized that insomnia can develop entirely from physiological activation, as in phase-shift insomnia or in individuals predisposed to physiological activation.

Several studies have found significantly increased physiological activation in patients with insomnia. Table 1 summarizes the psychological changes in insomnia patients. For example, Monroe *(6)* reported increased rectal temperature, heart rate, basal skin resistance, and phasic vasoconstrictions 30 minutes prior to and during sleep in patients with insomnia as compared to normal sleepers.

Other studies have shown that patients with sleep-onset insomnia had increased frontalis *(7)* and mentalis electromyogram (EMG) *(8,9)*, increased heart rate *(10,11)*, increased finger temperature, and more β and less α frequencies in the electroencephalogram (EEG) *(8,9)*. However, significantly elevated body temperature has not been reported in all studies of poor sleepers *(12,13)*. Poor sleepers have increased secretion of corticosteroids and adrenaline *(12,14)* compared with good sleepers in most, but not all, studies *(15)*.

The inconsistent results in some of these physiological activation studies may indicate that physiological activation is not a major factor in all patients *(16)* or that wide variability and small sample sizes may make it difficult to show clear physiological differences. It might be that lack of control of daytime activity in the studies obscured differences. It is also possible that the involved physiological system(s) differs from patient to patient and that more global measures, such as whole body oxygen use or heart rate variability, would more consistently show differences.

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Table 1
Reported Physiological Changes in Insomnia Patients

Physiological variable	Studies (ref. no.)
Increased body temperature	*6*
Increased heart rate	*6,10,11,26*
Increased sympathetic nervous system activity	*11*
Decreased parasympathetic nervous system activity	*11*
Increased EMG	*7–9*
Increased EEG β	*8,9*
Decreased EEG α	*8,9*
Increased corticosteroids	*12,14*
Increased adrenaline	*14*
Increased $\dot{V}O_2$	*24,25*
Increased skin resistance	*6*
Increased phasic vasoconstrictions	*6*
Increased daytime sleep latency	*20, 21, 24*

EMG, electromyogram; EEG, electroencephalogram.

Other research has examined daytime function in patients with insomnia to verify subjectively reported deficits in performance, mood, and alertness. The cumulative partial sleep deprivation that should arise from chronic insomnia should produce daytime sleepiness or increased susceptibility to acute sleep loss in patients with insomnia, but studies have consistently found that these patients are not sleepier than normal controls on the Multiple Sleep Latency Test (MSLT) *(13,17,18)* or after sleep loss *(19)*. These individuals may actually have longer MSLT latencies *(20,21)*.

Studies have found that patients with insomnia made more errors on a line-tracing task *(22)*, produced fewer responses in a word category test *(13)*, and performed worse on the Romberg (balance) test *(23)*. However, such deficits may have reflected that elevated arousal reduces steadiness or blocks higher order associates. Studies that compared daytime performance of insomnia patients to performance of normal controls have generally not found differences on tests that are sensitive to sleep loss *(18,23)*. Based on these results and on patient reports that they are fatigued or "washed out" during the day, it has been hypothesized that standard sleep and sleep-loss tests are confounded in that they "simultaneously measure sleep need and hyperarousal, which is interfering with sleep onset" (p. 59) *(20)*. This concept is supported by studies *(18,20,22)* that reported significant negative correlations between total sleep at night and MSLT values the next day.

With this background in mind, we planned a series of experiments to define more general measures of physiological activity in patients with psychophysiological insomnia and to differentiate causal factors in the production of both poor nocturnal sleep and compromised daytime function. This chapter reviews our work to define metabolic and cardiac changes in patients with insomnia and the relationship of such physiological changes to poor sleep and the report of insomnia.

EXPERIMENTAL

Metabolic and Cardiac Change in Insomnia Patients Compared with Normal Controls

Several similar studies were initially performed to compare sleep and physiological measures of patients with psychophysiological insomnia and sleep state misperception (SSM) with matched normal sleepers. It was hypothesized that patients with both psychophysiological insomnia and SSM insomnia would differ from controls by having increased physiological activation independent of their sleep-stage parameters. The same general screening criteria were used for all studies. Subjects were required to be healthy, 18- to 50-year-old males and females.

Patients with Insomnia

Individuals we considered indicated that they had a sleep problem, that it took them no less than 45 minutes to fall asleep at least 4 nights each week, or that they were awake no less than 60 minutes each night after falling asleep for at least 4 nights each week for at least 1 year. Patients with insomnia were also required to have EEG sleep latencies (SLs) greater than 30 minutes on 2 consecutive lab nights or to have a sleep efficiency of less than 85% on both nights.

Patients with SSM

Patients with a complaint of insomnia who demonstrated normal sleep (SL < 30 minutes and sleep efficiency > 90%) despite their claim of insomnia, overestimated their SL by at least 100% on both sleep laboratory nights, and had SL estimates of 20 minutes or longer on both nights were considered.

Normal Sleepers

Subjects with reported normal sleep were selected to match a qualified insomnia patient by gender, age (within 5 years), weight (within 25 pounds), and general time in bed (TIB) characteristics. Subjects were also required to have EEG SLs less than 30 minutes on 2 consecutive laboratory nights and to have a sleep efficiency greater than 90% on both nights.

Exclusions

Potential subjects who indicated excessive caffeine consumption (more than 250 mg of caffeine per day), who were using psychoactive medication or drugs, or who had completed a drug or alcohol abuse program within the previous year were excluded. Individuals with a history of depression or psychiatric hospitalization were excluded. Potential subjects who had histories strongly suggestive of circadian desynchrony (e.g., shift workers), sleep apnea, or periodic leg movements (PLMs) were excluded. Subjects with an apnea/hypopnea index or a PLM arousal index greater than 10 were disqualified.

Design

Subjects spent 2 nights and the intervening day in the laboratory. On both nights, a standard clinical polysomnogram was performed. On the second night, metabolic measures, including $\dot{V}O_2$ were recorded.

On the day spent at the laboratory, subjects had a 20-minute metabolic observation after awakening, performed computer tests, took an MSLT followed by 20-minute resting metabolic observations, and completed a Minnesota Multiphasic Personality Inventory (MMPI) test and a sleep history. They were fed the same daily menu of food prepared at the laboratory. Caffeinated beverages were not available.

Metabolic Rate in Psychophysiological Insomnia and SSM

Groups of 10 patients with psychophysiological insomnia and matched normal sleepers who did not differ in age, weight, or time usually spent in bed per night were identified *(24)*. As expected by selection criteria, patients with insomnia had significantly longer objective SLs (20.5 vs 12.5 minutes) and shorter total sleep time (TST) per night (342 vs 442 minutes) compared to the matched controls.

The initial analysis was based on mean $\dot{V}O_2$ data for each minute across the night. Each subject was compared to a matched control minute-by-minute by *t*-test. The *t* values from each of the 10 subject pairs were in the same direction, and 9 of 10 were statistically significant ($p < 0.01$). The average *t* value was 13.10 with 475 degrees of freedom (df) ($p < 0.0001$). The respective means for $\dot{V}O_2$ for insomnia patients and normal subjects were 296 and 266 mL/min.

In a second set of 10 *t*-tests with awakenings, movements, and arousals eliminated from the data set, 9 *t* values were in the predicted direction, and 8 of 10 were statistically significant ($p < 0.02$). The average *t* value was 13.38 with an average of 140 df ($p < 0.0001$). The overall mean sleep metabolic rates for the insomnia and normal groups, respectively, were 280 and 256 mL/min.

When only slow-wave sleep (SWS) was examined, it was found that two subjects (one insomniac and one normal subject) had no stage 3 or 4 sleep. Because the two subjects were in different pairs, those pairs were eliminated, and the SWS analysis proceeded on the eight pairs of subjects who all had SWS. In the set of eight *t*-tests comparing metabolic values from SWS observations between matched insomnia patients and normal subjects, seven *t* values were in the predicted direction, and five of eight were statistically significant. The average *t* value was 5.57 with an average of 51 df ($p < 0.0001$). The overall mean sleep metabolic rates for the insomnia and normal groups, respectively, were 266 and 250 mL/min.

SSM

Groups of nine patients with SSM insomnia and matched normal sleepers who did not differ in age, weight, or TIB per night were identified *(25)*. As expected by subjective historical report of sleep, patients with SSM insomnia reported significantly longer SLs (98 vs 18 minutes) and shorter TST per night (5.3 vs 7.4 hours).

In the sleep laboratory, the patients with SSM estimated that their SL was significantly longer than the normals (52 vs 24 minutes), that their TST during the night was significantly shorter than the normal subjects (6.8 vs 7.5 hours), and that their sleep quality was significantly worse than the normal subjects. However, the

patients with SSM did not differ significantly from the normal subjects on any EEG sleep variable. In fact, TST was nonsignificantly longer in the patients as compared to the normal sleepers.

The mean $\dot{V}O_2$ for each of the eight waking metabolic measurements and the mean $\dot{V}O_2$ for each hour during the sleep period were entered into a repeated measures analysis of variance (ANOVA) with terms for the matched subjects (1 df) and time (15 df). The time by group interaction was not significant, but both of the main effects were significant. $\dot{V}O_2$ overall was elevated in the patients with SSM as compared to their matched controls ($F_{1,143} = 45.22$, $p < 0.001$). The means for the groups were 304 mL/min (SD 26) and 286 mL/min (SD 34).

Heart Rate and Heart Rate Variability

Groups of 12 patients with psychophysiological insomnia and matched normal sleepers who did not differ in age, weight, or usual TIB per night were identified *(11)*. As expected by selection criteria, patients with insomnia had significantly longer SLs (16.4 vs 6.6 minutes) and shorter TST per night (382 vs 445 minutes) compared to normal sleepers.

Nocturnal heart data were examined for both groups by dividing each night into 5-minute blocks based on sleep stage. No significant interaction was found between group and sleep stage. There was a significant main effect for Group for both beat-to-beat interval ($F_{1,44} = 44.67$, $p < 0.001$) and the interval standard deviation ($F_{1,44} = 56.16$, $p < 0.001$). The intervals were significantly longer (i.e., heart rate was lower) and the variability was greater in the normal subjects as compared to the patients with insomnia. Heart rate during wake, stage 2, and rapid eye movement (REM) sleep were, respectively 61, 58, and 59 beats per minute (BPM) for normal subjects and 68, 64, and 68 BPM for the patients with insomnia. Several previous studies showed increased heart rate in patients with insomnia as compared to normal sleepers during the night. Monroe *(6)* reported a nonsignificant 3.9 BPM increase for patients with insomnia, Stepanski et al. *(26)* reported a significant 4.4 BPM increase for patients with insomnia, and Haynes and co-workers *(10)* reported a significant 4.6 BPM increase for patients with insomnia compared to normal sleepers. These reported differences agree well with the data from the present groups, for which the overall mean difference in heart period translated to a heart rate difference of 6.9 BPM.

The same 5-minute blocks of digitized heart data were analyzed by spectral analysis to provide estimates of low frequency and high frequency spectral power. ANOVA indicated that the interaction F value for group by stage was not significant for either low-frequency power (LFP) or high-frequency power (HFP) ratios ($F_{3,33} = 1.407$, NS and $F_{3,33} = 1.766$, respectively). There was a significant main effect for group for both LFP ($F_{1,32} = 12.93$, $p < 0.001$) and HFP ($F_{1,44} = 12.21$, $p < 0.001$). These results indicated that LFP was increased and HFP was decreased in patients with insomnia compared to normal sleepers across all sleep stages.

SUMMARY

These metabolic and heart rate data replicated previous studies that indicated elevated levels of physiological arousal in patients with insomnia. The finding of elevated $\dot{V}O_2$ elevated heart rate, and altered heart rate variability within sleep stages strengthened the case that the elevated levels of arousal were not simply a by-product of poor sleep. Finally, elevated metabolic rate in patients with SSM showed that these patients truly do have an objective, physiological problem as the basis of their complaint despite the fact that their sleep stage distributions were normal. These physiological findings were supported very recently by a spectral analysis of EEG of patients with SSM *(26a),* which showed increased higher frequency EEG in these patients. Such physiological findings support underlying hyperarousal as a causal mechanism in the sleep complaints presented. The findings of significant changes in heart rate variability in patients with insomnia also are consistent with elevated sympathetic nervous system activity and decreased parasympathetic nervous system activity.

As an entity, insomnia is infrequently viewed as a significant medical problem. However, if insomnia is associated with chronic sympathetic hyperactivity, long-term consequences of the sympathetic activation associated with the insomnia may exist. Many risk factors for coronary heart disease are related to increased sympathetic activity. For example, hypertension; elevated plasma insulin *(27)* and its related decrease in high-density lipoprotein (HDL) cholesterol and increase in triglycerides and cholesterol *(28)*; increased hematocrit *(29)*; decreased plasma volume *(30)*; increased plasma thromboglobulin *(31)*; increased plasma angiotensin *(32)*; and increased cardiac arrhythmias *(33,34)* are all signs of increased sympathetic and decreased parasympathetic tone. It remains to be determined if patients with chronic insomnia are also at increased risk for these disorders.

Effects of Physiological Activation

In addition to poor sleep, it has been established that many patients with insomnia will report daytime fatigue or dysphoria, have normal or longer than normal MSLT values, report increased stress, have abnormal MMPI values, and subjectively misperceive their sleep process. These findings are summarized in Table 2.

Because patients with insomnia typically display both mood alteration and evidence of physiological arousal, differentiation of cognitive vs physiological pathology as the primary causal factor has been difficult. Production of consistent and long-lasting mood changes in normal individuals to test the effect of mood change on sleep and daytime function is difficult. However, in one study, it was possible to produce a state of chronic physiological activation and to follow these hyperaroused normal individuals for the development of both nocturnal and daytime symptoms of insomnia *(35)*.

In that study *(35)*, 400 mg of caffeine was given three times a day to 12 normal young adult sleepers for 1 week as a means of increasing physiological arousal, and

Table 2
Variables that Differentiate Insomnia Patients vs Normal Sleepers Given Caffeine or the Sleep on an Insomnia Patient. Data from Normal Sleepers Who Had Situational Insomnia are also Reported.

	True insomnia	Hyperaroused normal subjects	"Yoke" insomnia normal subjects	Situational insomnia
MSLT	Increased	Increased[a]	Decreased[b]	Increased[c]
Metabolic rate/ heart rate	Increased	Increased[a]	Increased PM[b]; decrease AM	Increased[c]
Body temperature	Increased	Increased	Decreased[b]	No measure
Mood (tension, confusion)	Increased	Increased[a]	Decreased[b]	No change
Vigor	Decreased	Decreased[a]	Decreased[b]	No change
Personality disturbance	Increased	Increased MMPI PT[a]	No change	No change
Subjective sleep latency/wake	Overestimated	Mild overestimation	No change	No change

[a]Significant differences reported in ref. *35*.
[b]Significant differences reported in ref. *36*.
[c]Significant differences reported in ref. *45*; MSLT, Multiple Sleep Latency Tests; MMPI PT, Minnesota Multiphasic Personality Inventory Psychasthenia (Anxiety) Scale.

standard insomnia outcome variables were measured. As expected, chronic use of caffeine significantly increased whole body metabolic rate, which was used as the objective measure of arousal level, and sleep efficiency declined significantly.

It is well known that caffeine can produce poor sleep. However, the major question in this study was whether caffeine would also produce the other secondary effects seen in chronic psychophysiological insomnia.

Responses from the Profile of Mood States (POMS) suggested increasing dysphoria as caffeine administration progressed (*see* Table 2 for a summary of caffeine effects). Significant main effects for condition were found for all six POMS scales. Initial caffeine administration produced an immediate significant increase in vigor and tension (anxiety), followed by a decrease as caffeine administration continued (significant for vigor). Fatigue was significantly increased at the end of caffeine administration compared to placebo. These results were of considerable interest because they showed that the chronic daytime dysphoria and fatigue reported by patients with insomnia could be paradoxically produced by unrelenting physiological arousal.

The MSLT data revealed that SLs were significantly increased throughout caffeine administration compared to baseline and withdrawal, which did not differ. The mean SL after early caffeine use was significantly longer than the SL after

chronic caffeine use. Respective means for baseline, early caffeine, late caffeine, and withdrawal were 10.7, 17.9, 13.4, and 11.3 minutes, respectively. Again, these increased SLs were similar to those seen in insomnia patients compared with normal subjects.

The MMPI is a nontransparent measure of relatively stable personality characteristics. It was administered before caffeine use and at the end of the caffeine administration primarily because it has been used as a measure in many previous insomnia studies. At baseline, as expected, all of the MMPI values were characteristic of normal young adults. However, after 1 week of caffeine administration, there was movement toward increased pathology on all the clinical scales except masculine–feminine scale, and the change was statistically significant for the Psychasthenia (anxiety) scale. These findings were also surprising because they indicated that even stable aspects of personality could shift significantly toward pathology in a short period secondary to a relatively simple physiological manipulation.

As can be seen in Table 2, subjects given caffeine had significant changes in the direction of patients with chronic insomnia on MSLT, metabolic rate, negative moods, and personality. The data indicate that chronic hyperarousal with no predisposing psychological component can produce the typical pattern of poor sleep, mood change, and personality change commonly seen in patients with psychophysiological insomnia. However, it could not be determined from these data if the mood and personality symptoms were produced by the hyperarousal or were secondary from the poor sleep also produced.

Effects of Poor Sleep

It has been implied that increased physiological arousal, possibly even as an innate phenomenon, produces an environment in which an individual is prone to report insomnia. Many patients with insomnia, however, feel that their sleep is the central problem, and that poor sleep leads to symptoms of fatigue and dysphoria. To test whether the insomnia sleep pattern by itself could produce hyperarousal and the other symptoms of primary insomnia, the poor sleep found in patients with insomnia was produced for 1 week in normal young adults, and subjects were followed for the development of insomnia symptoms *(36)*. Patients with primary insomnia were identified based on the same report of poor sleep and polysomnographic criteria as used for insomnia patients who participated in the metabolic studies reported earlier and the sleep parameters of those patients were used in a yoke control fashion to produce comparable sleep in a group of matched normal sleepers. It was hypothesized that if the yoked normal sleepers developed the spectrum of secondary symptoms seen in the patients with "true" insomnia after sleeping like the patients, then those symptoms could be seen as secondary to the poor sleep. On the other hand, if the yoked normal sleepers did not develop the symptoms seen in the true patients with insomnia, then some factor other than poor sleep itself would be responsible for those secondary symptoms.

In this study, the EEG sleep characteristics of patients with primary insomnia were reproduced in matched normal sleepers for a week. Sleep patterns were matched by making experimental arousals and awakenings throughout the night in normal sleepers to match the pattern of wake time and arousals seen in the patients with insomnia. Because the EEG sleep produced in the study was similar to that found in patients reporting insomnia, changes in the outcome variables should have reflected the consequences of pure "poor" sleep. Table 2 provides a summary of typical findings for patients with insomnia and compares those findings with the results of this yoke control study.

Changes secondary to the poor sleep produced in the yoke control study were clearly different from the symptoms most frequently reported by patients with insomnia. Patients with insomnia typically have difficulty falling asleep both at night and during the MSLT *(20–22,24)*. However, both SL and MSLT data from the yoke control study supported significantly increasing ease of falling asleep as the nights of insomnia increased.

Patients with insomnia frequently have elevated body temperature and whole body metabolic rate *(6,14,24)*. Except for an increase in nocturnal metabolic rate probably associated with the experimental sleep disturbance itself *(37)*, the trends in the yoke control study showed lower metabolic rate and decreased body temperature during the day. Patients with insomnia typically report increased stress, anxiety, or depression *(1,24)*. However, in the yoke control study, the state measures of tension and depression decreased significantly during the study. Patients with insomnia typically have elevated MMPI scales, but the MMPI measures were unchanged in this study. Patients with insomnia report increased fatigue and decreased vigor, and similar changes were found in the yoke control study. However, these changes are also found during simple sleep deprivation.

Finally, patients with insomnia overestimate their time spent awake during the night. Despite increased awakenings and wake time in the yoke control study, the normal sleepers continued to correctly estimate their wake time during the night.

The most parsimonious explanation for the results was that the insomnia sleep pattern resulted only in partial sleep deprivation when imposed on normal sleepers. This interpretation is supported by rebounds of REM and SWS during the recovery night after the 7 nights of yoke insomnia and by decreasing MSLT values. These changes are classic signs of sleep loss. Decreases in vigor and body temperature also suggested simple sleep loss. Because TST in the study was reduced to 6 hours each night for a week, this could easily have resulted in partial sleep deprivation. For example, a study by Rosenthal et al. *(38)* showed increased sleepiness on the MSLT after just 1 night of 5.6 hours of sleep.

The data from the yoke control study support the contention that some patients with insomnia may suffer from mild partial sleep deprivation. As in normal subjects, however, the degree of deficit should be related to the amount of sleep lost and should typically recover after an occasional night of improved sleep. In fact, one could hypothesize that poor sleep in response to hyperarousal is an adaptive

response that acts as a homeostatic mechanism to cause partial sleep deprivation and reduce the impact of hyperarousal. Unfortunately, in patients with chronic insomnia, a night of relatively good sleep would remove a portion of the chronic partial sleep deprivation and leave the patient more susceptible to the effect of hyperarousal. This situation leaves patients in the uncomfortable situation of suffering either from hyperarousal or from hyperarousal masked by sleep deprivation.

If the poor sleep of patients with insomnia produces only mild sleep loss in matched normal sleepers, how does one explain the consistent secondary symptoms reported by patients with insomnia? As can be seen from Table 2, the secondary symptoms of patients with insomnia appear in normal sleepers who are hyperaroused *(35)*, but not in normal sleepers actually given the poor sleep experienced by patients with insomnia. The major implication of such data is that it is the increased arousal and not the poor sleep *per se* that is responsible for the symptoms. Is it possible, however, that the development of symptoms in patients with insomnia is actually dependent on poor sleep interacting with personality variables in the patients with insomnia? If this is the case, then one would expect that patients with insomnia who have particularly poor nights of sleep would experience an exacerbation of their insomnia symptoms.

In another study *(39)*, it was hypothesized that, if nocturnal sleep parameters produced the daytime dysphoria reported by patients with insomnia, then patients with sleep maintenance insomnia who were kept awake even longer than usual during the night should have had increased dysphoria during the following day. To test this hypothesis, patients with sleep maintenance insomnia were allowed only 80% of their already reduced TST each night for 7 consecutive nights. This sleep reduction was accomplished by waking patients up at the end of each quarter of the night if they accumulated more than 80% of their baseline sleep for that quarter of the night (while holding TIB for the entire night at the baseline level). This paradigm produced very poor sleep (average TST of 4.2 hours on each night for the week).

This reduction of TST by experimental awakenings resulted in a significant decrease in daytime MSLT values for these insomnia patients. After 7 nights of 4.2 hours of sleep, MSLT values decreased from 15.6 to 11.1 minutes. Although this reduction was statistically significant, the 11.1-minute value was still within the normal range for the test.

In a study in which total sleep was reduced to 5 hours per night in normal young adults *(40)*, MSLT was reduced to 41% of baseline compared to a reduction to 71% of baseline that was found for the patients with insomnia. These results indicated that when the sleep of insomnia patients was experimentally reduced, they displayed some increased sleepiness during the day, in agreement with the expectancy in normal sleepers, but not the increased latency typical in patients with insomnia as their nocturnal sleep worsens. Despite the large reduction in TST, the patients with insomnia did not become pathologically sleepy on the MSLT, and this probably indicated the degree to which their hyperarousal was successful in masking

their sleep tendency. Of equal interest, patients did not report significant decreases in their sleep quality or show changes in personality or physiological parameters consistent with more severe insomnia when their wake time during the night was increased by 2 hours.

One conclusion from such data is that the reports of poor sleep quality and daytime dysphoria from patients with insomnia are not directly related to their EEG sleep, but rather to their level of arousal *(41)*. In support of these results, Chambers and Kim *(42)* reported a significant negative correlation between state anxiety at bedtime and reports of feeling rested on the next day for patients with insomnia despite the fact that neither anxiety nor reports of feeling rested were significantly correlated with sleep values.

Level of Arousal and the Perception of Sleep

Insomnia patients commonly overestimate how long it takes to fall asleep at night and underestimate their TST. Is such misperception related to personality or to underlying physiology? We decided to look at several physiological manipulations to determine if they produced changes in the perception of sleep onset *(43)*.

Patients with insomnia subjectively estimate that it takes much longer to fall asleep than EEG measures indicate *(44)*. One means of examining this phenomenon is to divide the subjective estimate of SL by the EEG estimate to derive a unitless indicator of degree of estimation difference. For example, sleep deprivation or the use of benzodiazepines decreases the level of arousal and was hypothesized to decrease this subjective to objective ratio of SLs. Conversely, administration of caffeine, which increases arousal level, or sleep during the daytime, when level of arousal is higher, should increase the ratio.

Specifically, results from several studies *(43)* indicated that the ratio of subjective to objective SL decreased when subjects were given triazolam or diazepam to decrease level of arousal, and the decreases tended to be dose related. Similarly, the ratio of subjective to objective SL decreased during sleep deprivation; again, the decreases were related to the amount of sleep lost. In two tests of increased arousal, the ratios of subjective to objective SLs increased after an initial night of caffeine consumption and were greater during sleep periods that began midday than in sleep periods that began later in the evening. These data supported the contention that the perception of falling asleep was related to the level of physiological arousal at sleep onset. The consistency of the findings with six different experimental manipulations supports the argument that estimates of SL may also be dependent on level of physiological arousal.

These data support the idea that subjectively reported poor sleep or insomnia is a physiological phenomenon that can be controlled by varying the level of arousal. The point is that poor sleep, whether it is acute or chronic, is a physiological (as opposed to a psychological) event that is amenable to physiological exploration and modification.

The Development of Insomnia

It is well known that the incidence of insomnia increases with age. This increase could be associated with increasing sympathetic nervous system dominance that is also associated with age or with cognitive or behavioral changes. Unfortunately, very little empirical work has examined how insomnia starts or develops. One theory holds that individuals placed in a situation of temporary stress develop poor sleep hygiene or inappropriate conditioned responses to their sleep environment. Then, the poor hygiene or inappropriate responses continue to produce poor sleep after the period of stress passes.

If this is true, one way to understand the development of insomnia would be to take normal young adults, expose them to a temporary stress, and evaluate the insomnia produced.

We specifically followed this methodology in a recent study of 50 normal sleepers exposed to a series of stressful experiences, including first night in a sleep laboratory, 3-hour phase advance of sleep time, 6-hour advance of sleep time, and sleep following administration of 400 mg of caffeine 30 minutes prior to bedtime *(45,46)*.

It was found that there was both wide variability and remarkable consistency in the responses seen. The variability was in the between-subject response to the situational stress—some subjects continued to have nearly normal nights of sleep even after a 6-hour phase advance of bedtime or caffeine ingestion, whereas other individuals had poor sleep following all of the stresses. This study involved so many participants that it was possible to form "extreme" groups—in this case the 25% of the population that slept best on the first night in the laboratory (super sleepers) and the 25% who had the worst sleep on that night (situational insomnia [SI]). Significant correlations were found between sleep efficiency on the first night and on the other stress nights in the complete data set and also by comparing sleep values in the extreme groups.

Subjects who had poor sleep on their laboratory adaptation night (and were therefore called the SI group) also had increased MSLT on the day that followed. They had normal sleep on the baseline night that followed, but then had significantly worse sleep on the phase-advance nights and after caffeine administration. Their sleep was so bad after the 6-hour phase advance (about 4.5 hours compared with about 7 hours for the super sleepers) that their MSLTs were significantly reduced on the day that followed. The SI group also had very poor sleep after caffeine administration but surprisingly, the MSLTs after caffeine administration were significantly increased. The super sleep group did not have any significant changes in MSLT throughout the study. The implication is that the SI group was not only more sensitive to all of the stresses in terms of the production of poor sleep, but also was more sensitive to the arousing effect of caffeine.

This study also examined other differences between the SI and good sleeping groups (*see* Table 2). No significant differences were found on the MMPI or mood measures. Whole body metabolic rate was nonsignificantly increased in the SI group. The SI group was found to have increased heart rate, increased LFP and

decreased HFP compared to the good sleepers. These physiological findings in "preinsomnia" patients suggest that their existing hyperreactivity to sleep-related stress and caffeine could be secondary to elevated sympathetic nervous system activity, and this could be a marker for the development of chronic insomnia at a later date. The finding of elevated physiological activity prior to mood change, personality change, or complaint of chronic insomnia provides another clue that underlying physiology could be the key to the later development of additional insomnia symptoms.

DISCUSSION

It is generally accepted that there are changes in several physiological systems in association with psychophysiological insomnia. The current experiments attempted to refine our understanding of the relationship among physiological arousal, poor EEG sleep, psychological status, and subjective report of insomnia. The finding that experimentally produced chronic physiological arousal in normal young adults produces the mood and personality changes seen in patients with insomnia provides a compelling description of how chronic insomnia could develop in physiologically susceptible individuals. The studies showing that, by itself the poor sleep of patients with insomnia does not produce the arousal, mood, and personality characteristics of patients and that the production of much worse EEG sleep in patients with insomnia does not magnify symptoms leads to the conclusions that the symptoms produced by chronic physiological arousal were not mediated by the poor sleep that was produced and the symptom complex that was associated with psychophysiological insomnia is not really a sleep disorder, but rather an arousal disorder. Finally, the importance of physiological arousal as the harbinger of insomnia was enhanced by the finding of elevated heart rate and abnormal cardiac spectral activity in normal subjects with no sleep complaint who were found to have EEG-defined SI. These several approaches identify tangible physiopathology that should be open to identification and amenable to treatment.

We have recognized for many years that some patients have lifelong problems with excessive sleepiness secondary to disorders such as narcolepsy or idiopathic hypersomnolance. The extent to which these disorders demonstrate a failure of the sleep system vs a failure of the arousal system can be debated. Certainly, these disorders are commonly treated with medications that have direct impact by increasing central nervous system arousal. Recognition that another group of patients suffers from the opposite lifelong problem (hyposomnolence or hyperarousal) has been more difficult. At this point, much work has identified the physiological markers of chronic hyperarousal in patients. Behavioral relaxation techniques can provide effective help for patients with some situational hyperarousal, but as behavioral techniques such as sleep extension eventually fail in patients with idiopathic hypersomnolance, behavioral techniques may also fail in patients suffering from chronic hyperarousal. Identifying arousal disorders as a major component of both hypersomnolance and insomnia can help direct research toward more effective pharmacological control of the underlying physiologic arousal disorder.

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4

Differential Diagnosis of Insomnia

Hrayr P. Attarian

Not poppy, nor mandragora,

Nor all the drowsy syrups of the world,

Shall ever medicine thee to that sweet sleep

Which thou owedst yesterday.

—William Shakespeare (1564–1616) "Othello. Act iii. Sc. 3"

DEFINITION

Insomnia is the inability to obtain sleep of sufficient length or quality to produce refreshment the following morning. It is not defined by total sleep time per 24 hours. For example, a person who needs only 4 hours of sleep does not have insomnia if he or she is refreshed in the morning after having 4 hours of sleep, whereas someone who needs 10 hours of sleep may have insomnia if he or she does not feel refreshed even after 8 hours of sleep *(1)*. Contrary to popular belief, psychiatric or psychological factors are not the most common causes of insomnia *(1)*. In fact, untreated insomnia, itself, is a risk factor for the subsequent development of clinical depression and psychiatric distress *(2)*.

Insomnia is not a diagnosis in and of itself. It should be thought of as a constitutional symptom, not unlike pain, fever, or weight loss, requiring identification of an underlying cause before diagnosis and a treatment plan are established *(1)*.

TYPES OF INSOMNIA AND UNDERLYING CAUSES

Disorders causing insomnia can be divided into two major categories: primary and secondary. Primary insomnia is when the insomnia is the major or sole symptom of a disorder. Insomnia is considered secondary when it is a symptom of an underlying medical or psychiatric illness (Table 1).

From: *Current Clinical Neurology: Clinical Handbook of Insomnia*
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Table 1
Types of Insomnias

Primary insomnias	Secondary insomnias
Psychophysiologic, or conditioned, insomnia	Insomnia in psychiatric illnesses
Idiopathic, or childhood-onset, insomnia	Insomnia in other sleep disorders
Sleep state misperception insomnia	Insomnia in neurological disorders
Poor sleep hygiene insomnia	Insomnia in medical disorders
Other extrinsic insomnias	Medication-induced insomnia
Fatal familial insomnia	Menopause-related insomnia
	Environmentally induced insomnia
	Restless legs syndrome

Psychophysiological, or Conditioned, Insomnia

This is the most common form of insomnia and is typically acquired during a period when other factors (e.g., stress) are at work. After a few days of sleeping poorly, the patient becomes concerned and begins trying harder to get to sleep. The result is arousal and aggravation of the insomnia. Stimuli surrounding bedtime (e.g., the bedroom, the bed itself) may become triggers to arousal. Thus, such patients may have severe problems with sleep in their own bedrooms but may sleep remarkably well in other locations (e.g., on the living room couch, in a motel, in a sleep laboratory). The essence of psychophysiological insomnia is that attention is focused on the inability to sleep. Insomnia is perceived as the only source of distress, and other emotional or mental concerns are minimized. Typically, patients repress or deny awareness of stress factors and see the insomnia as occurring without any reason.

In some patients with psychophysiological insomnia, no precipitating stress is found. Rather, poor sleep may have gradually developed as an occasionally occurring disturbed night leads to increased concern, causing sleep to deteriorate until it becomes the patient's chief concern. There is clear evidence for the role of familial inheritance in the tendency to develop insomnia *(3)*.

Idiopathic, or Childhood-Onset, Insomnia

This rare condition presents as a chronic, serious inability to initiate and maintain sleep, which can often be traced back to the first few weeks of life. Sleep latency (i.e., the time it takes to fall asleep after going to bed) may be very long, and sleep is riddled with awakenings. Daytime features typically include decreased attention and vigilance, low levels of energy and concentration, and deterioration of mood that is usually described as grim and subdued rather than obviously depressed or anxious. The presumed underlying neurological abnormality (either hyperactivity in the arousal system or hypoactivity in the sleep system) may vary from mild to severe, so the range of insomnia encountered also may vary from mild (essentially, the patient is a light sleeper) to severe and incapacitating *(4)*. In mild or moderate

idiopathic insomnia, psychological functioning is remarkably intact. In severe cases, daytime functioning may be severely disrupted, and affected patients may be unable to hold a job. During childhood and adolescence, idiopathic insomnia is often associated with dyslexia and hyperactivity. In many cases, diffuse, nonspecific abnormalities are seen on an electroencephalogram (EEG) *(4,5)*. There is no direct human evidence for structural neuropathology. Although idiopathic insomnia appears in childhood, not all childhood insomnia is idiopathic *(6)*.

Sleep State Misperception Insomnia

In this fascinating disorder, complaints of insomnia occur without any objective evidence of sleep disturbance. Patients may report that they have not slept at all in weeks, months, or years. However, on objective sleep studies, they sleep several hours per night *(7)*. When results of sleep evaluation are presented, patients with sleep state misperception (SSM) may vehemently insist that the studies are in error because they are convinced that they sleep very little, if at all.

Poor Sleep Hygiene

In some patients, insomnia is the result of lifestyle. In others, poor sleep hygiene develops as a result of chronic insomnia. For example, in the latter case, patients may begin to drink more coffee to remain awake during the day and more alcohol to fall asleep at night. They may stay in bed for extended periods in an attempt to get more sleep. However, such ploys only serve to perpetuate the insomnia *(5)*.

Fatal Familial Insomnia

This hereditary condition, with autosomal-dominant transmission, is characterized clinically by progressive insomnia, dysautonomia, dysphagia, dysarthria, diplopia changes in circadian rhythm of hormone secretion, motor signs, myoclonus, and slight to moderate deterioration of cognition. The usual age of onset is between 35 and 60 years, and the course of the illness is between 7 and 32 months. In this condition, an abnormal prion protein (PrPsc) is present in the brain, and there is mutation of gene coding for PrPsc. The fatal nature of this illness is due to neurological degenerative changes, not to the insomnia itself *(8, 9)*.

Restless Legs Syndrome and Periodic Limb Movement Disorder

These familial, common, and related conditions are found in varying degrees in up to 10% of the population *(10)*. The prevalence of periodic limb movement disorder (PLMD) is 3.9% and restless legs syndrome (RLS) is 5.5% *(11)*. The four cardinal symptoms of RLS are a desire to move the legs, accompanying paresthesias that are characterized as uncomfortable or indescribable, motor restlessness, and worsening of symptoms at night and at rest *(12)*. Symptoms of RLS may worsen with administration of antidepressants *(13,14)* and during pregnancy *(15)*. Periodic limb movements (PLMs) occur in 80% of patients with RLS *(16)*. They are repetitive, stereotyped movements recurring at 5- to 90-second intervals lasting usually

15 to 40 seconds. PLMs are not considered abnormal unless they lead to severe sleep disturbance or excessive daytime sleepiness, or both, in which case they form a separate intrinsic sleep disorder, PLMD *(10)*. RLS can be easily differentiated from primary insomnias by history due to the characteristic symptoms with which it presents. Insomnia as a result of PLMD may require the aid of a polysomnogram (PSG; *see* later) to make the correct diagnosis.

Other Sleep Disorders

Occasionally, insomnia is the presenting complaint in obstructive sleep apnea (OSA) syndrome. In a group of older adults with insomnia, a respiratory disturbance index (RDI) of at least 15 per hour was found in 29% of patients *(17)*. In another study of a large group of patients with insomnia, RDI of at least 30 per hour was found in 2.3% of patients vs 1.3% of controls *(18)*. The presence of excessive daytime sleepiness, snoring, and observed apneas raises the possibility of OSA syndrome.

In circadian rhythm abnormalities, patients sleep well but not at socially acceptable times *(5)*. Those with the advanced sleep-phase syndrome have excessive sleepiness in the evening and undesired early morning awakening. Those with the delayed sleep-phase syndrome have sleep-onset insomnia, excessive daytime sleepiness (particularly in the morning), or both. Other circadian rhythm abnormalities presenting with a variety of insomnia symptoms include irregular sleep–wake cycle, non-24-hour sleep–wake syndrome and sleep disturbances in blind individuals, and those resulting from social circumstances: jet lag and shift-work sleep disorder *(19)*. Having patients fill out sleep diaries or sleep logs during a 1- or 2-week period when they are free of social restrictions of their bedtime and wake time (going to bed whenever they are sleepy and getting up on their own without an alarm) helps make the diagnosis of circadian rhythm abnormalities.

Occasionally, narcolepsy presents as insomnia because 50% of patients with narcolepsy have disrupted sleep at night *(20,21)*. Again, excessive daytime sleepiness and ancillary symptomatology (sleep paralysis, hypnic hallucinations, and cataplexy) differentiate insomnia resulting from narcolepsy from the primary insomnias.

Neurologic and Medical Conditions

Conditions that can cause insomnia, among other symptoms, include neurodegenerative diseases *(22)*, pain, allergies *(23)*, gastroesophageal reflux *(24),* and asthma *(25)*. All of these can be easily differentiated from primary insomnias by history and physical exam.

Menopause-Related Insomnia

There is a high level of sleep disturbance occurring in about 42% of middle-aged women *(26)*. Although cross-sectional analyses indicate that sleep disturbance may be independent of menopausal status, transition into postmenopausal status is associated with deleterious changes in sleep among women not receiving hormone replacement therapy *(26,27)*.

Psychiatric Conditions

When anxiety permeates most aspects of functioning in patients with insomnia, generalized anxiety disorder is the usual diagnosis. In contrast, if anxiety is focused almost exclusively on poor sleep and its consequences on daytime functioning, psychophysiological insomnia is the typical diagnosis *(28)*

Insomnia due to affective disorders is sometimes difficult to differentiate from psychophysiological insomnia because a dysphoric mood, ascribed to the effects of poor sleep, often accompanies psychophysiological insomnia. The two conditions can often be distinguished on the basis of other "vegetative" signs, such as loss of appetite or libido or the typical diurnal fluctuation (worse in the morning) of depression *(28)*. In general, a diagnosis of psychophysiological insomnia is inappropriate if the patient fulfills criteria for any other Axis I or II diagnosis in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) *(29)*.

Medication-Induced Insomnia

Selective serotonin reuptake inhibitors *(30)*, stimulants, theophylline, prednisone, and two of the newer anticonvulsants, felbamate *(31)* (Felbatol) and lamotrigine *(32)* (Lamictal), may cause insomnia. Other medication or chemically related causes of insomnia include withdrawal from sedative agents, idiosyncratic reactions to other medications, and toxin-related reactions (e.g., alcohol, carbon monoxide *[33]*, inorganic mercury *[34]*, recreational drugs). A thorough list of the patient's medications and chemical exposures is essential for the evaluation of insomnia.

DIAGNOSTIC TOOLS

PSG and Multiple Sleep Latency Test

The PSG is a polygraph of EEG findings, eye movements, electromyography readings, oxygen saturation, limb movements, airflow, and chest and abdominal movements taken during sleep, usually for the entire night. According to the American Sleep Disorders Association (now the American Academy of Sleep Medicine), practice parameters polysomnography is not indicated in routine evaluation of insomnia, except when the diagnosis is uncertain and a primary sleep disorder is suspected and when insomnia does not respond to appropriate behavioral and pharmacological treatments *(35)*.

A Multiple Sleep Latency Test (MSLT) is a series of four or five opportunities, each separated by a 2-hour interval, to take a 15- to 20-minute nap. It is used to assess sleep latency and the possibility of such sleep disorders as OSA and narcolepsy. In primary insomnia, results of the MSLT are usually normal *(36)*.

Sleep Logs

A sleep log (Fig. 1) is a graph on which, for 2 to 3 weeks, the patient records bedtime, approximate sleep time, times and duration of awakenings during the sleep

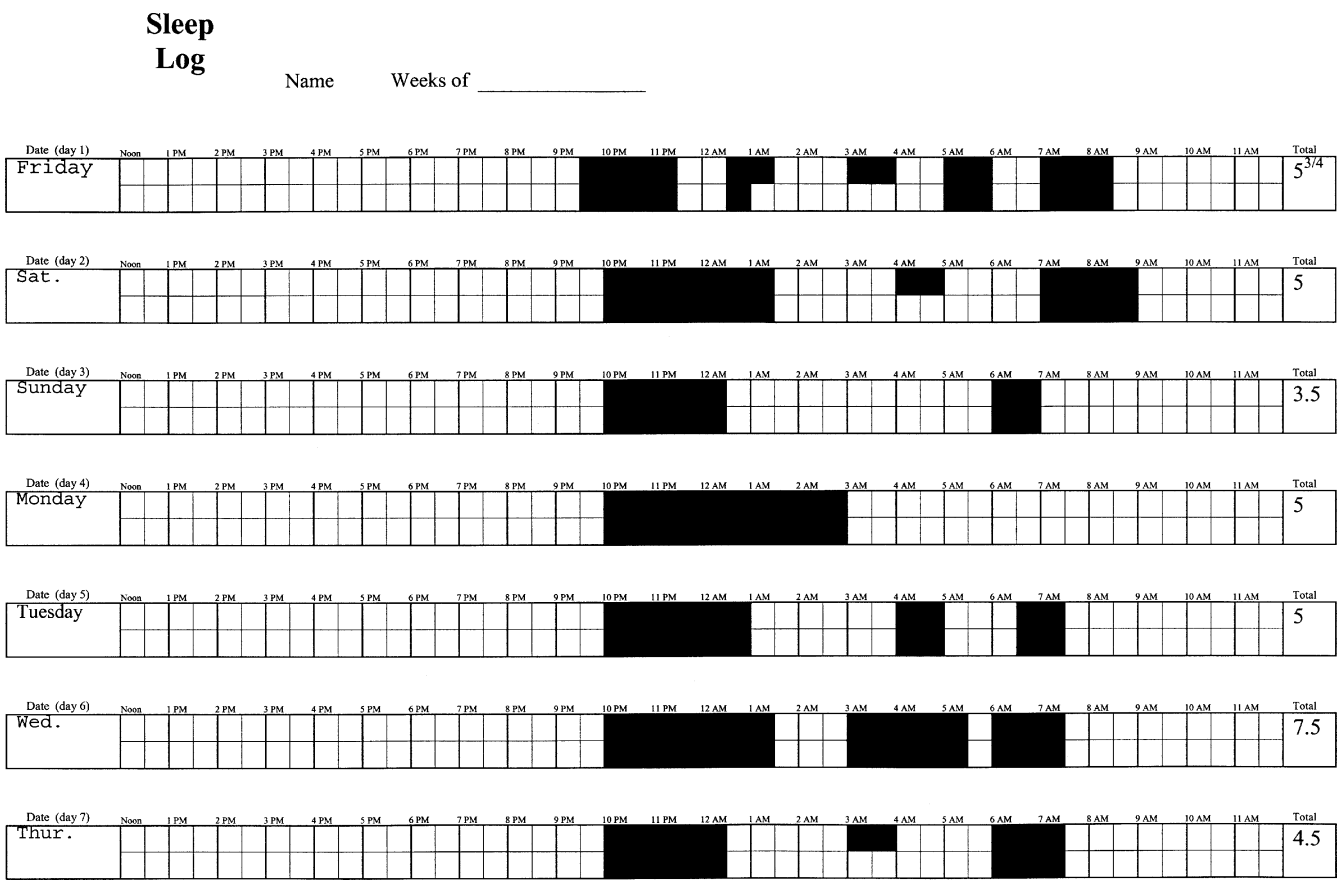

Fig. 1. Example of a 1-week sleep log. Shaged areas indicate sleep; open areas indicate wakefulness.

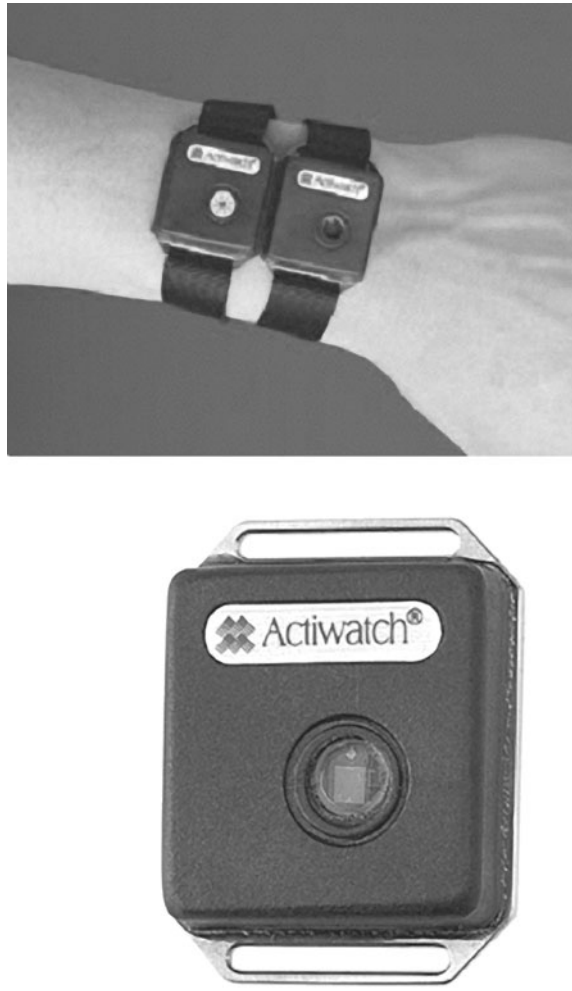

Fig. 2. Picture of an actigraph. (Used with permission. Courtesy of Mini Mitter® Co. Inc.)

period, final awakening time, and naps taken during the day. Although subjective, this record summarizes the patient's perception of the amount and quality of sleep he or she is getting *(37)*.

Actigraphy

Actigraphy is a recently developed technique to record activity during waking and sleeping without application of any electrodes. An actigraph (Fig. 2) is worn on the wrist and is about the size of a watch. It consists of a movement detector and considerable memory so it can record movement and nonmovement data plotted

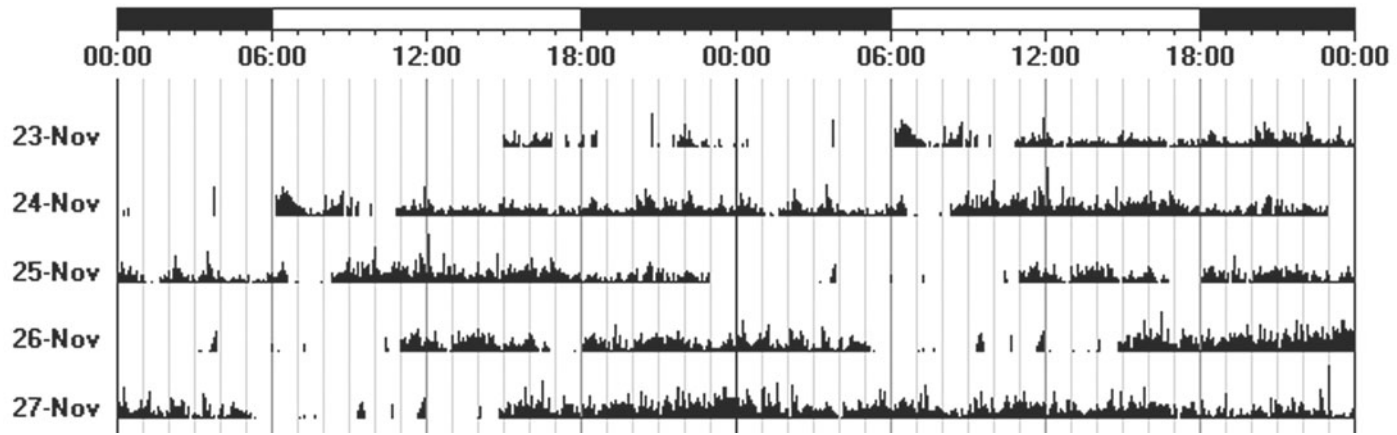

Fig. 3. One-week printout of an actigraph. High bars show wakefulness; low bars show sleep. (Used with permission. Courtesy of Mini Mitter Co. Inc.)

against time for 1 or 2 weeks. The patient can wear it continuously during sleep and as he or she goes about routine daily activities. Actigraphy is ideal for extended examination of the sleep–wake cycle in the patient's home environment. It is convenient and readily accepted by patients. It can be used to supplement sleep logs and to evaluate unusual complaints, such as, "I have not slept for several nights" *(1)*.

In general, patients have fewer limb movements during sleep than while awake. There is a very close correlation between the rest–activity findings recorded by the actigraph and the sleep–wake pattern as determined by a PSG. Several investigators used actigraphy in groups of controls of different ages and found minute-by-minute agreement in sleep–wake scoring between polysomnography and actigraphy to exceed 90% *(38)*.

Figure 3 depicts a 1-week printout of an actigraph.

Laboratory Evaluation

In patients with RLS, a serum ferritin level of less than 50 µg/L is associated with increased severity of symptoms, which may exacerbate insomnia *(39,40)*.

Diagnostic Workup

Insomnia is usually diagnosed by a thorough clinical history-taking. If anxiety permeates most aspects of functioning in patients with insomnia, then generalized anxiety disorder, rather than primary insomnia, is the usual diagnosis. Affective disorders can be differentiated from primary insomnia on the basis of other "vegetative" signs, such as loss of appetite or libido or the typical diurnal fluctuation (worse in the morning) of depression. In these situations, the patient should be first evaluated by a psychiatrist. If a history of significant dysesthesias interfering with sleep is elicited during history-taking, then the diagnosis of RLS should be considered, serum ferritin checked, and treatment initiated accordingly. The complaint of excessive daytime sleepiness manifested by falling asleep unintentionally or having a hard time staying awake in sedentary situations, is generally indicative of another primary sleep disorder, because patients with insomnia are hyposomnolent and often complain bitterly of the inability to take naps *(36)*. Patients reporting episodes of falling asleep unintentionally during the day should be evaluated with a PSG and an MSLT to rule out primary sleep disorders. Taking a history of the patient's sleep habits is essential in identifying sleep hygiene issues or circadian rhythm abnormalities. If the patient is unable to fall asleep at a desired time but is able to fall asleep much later and is unable to wake up at a desired time then the diagnosis of delayed sleep phase should be considered. If the patient is waking up very early in the morning and is unable to go back to sleep but cannot stay awake past early evening, then advanced sleep-phase syndrome should be entertained as a diagnosis. In short, if the patient is able to fall asleep but not at socially acceptable times, then the most likely cause of the complaint of insomnia is circadian rhythm abnormalities that can be treated with a combination of chronotherapy, phototherapy, and melatonin. A history of other medical problems, exposure to toxins,

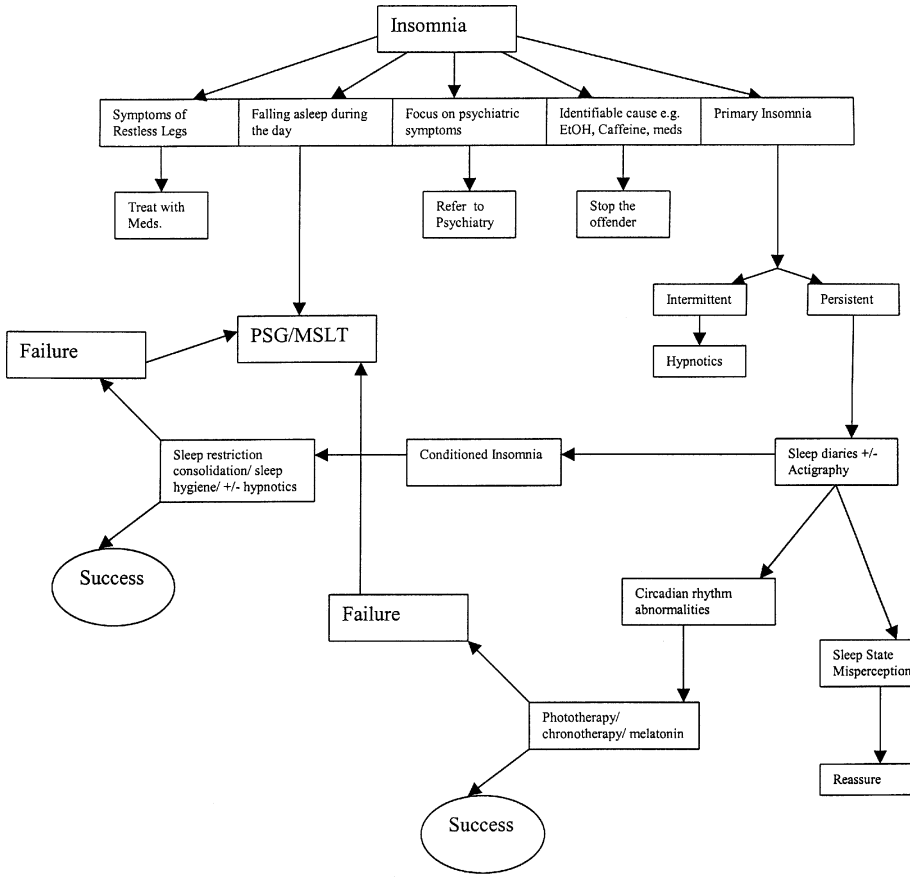

Fig. 4. Algorithm. (Used with permission. Courtesy of Primary Care Reports/American Health Consultants *[41]*.) Abbreviations: PSG, plysomnograph; MSLT, Multiple Sleep Latency Tests.

and a list of medication the patient is taking is also important because many chemicals, either pharmaceutical or toxic, can affect sleep and cause insomnia. If the diagnosis of persistent primary insomnia is made, then sleep diaries are essential in tailoring treatment to the individual patient's needs. An actigraph is an essential tool in primary insomnia; both in providing an objective measure of the true extent of the insomnia and for gauging response to treatment. In patients with intermittent situational insomnia, such as Sunday night insomnia, the use of hypnotic medication as the sole method of treatment is encouraged. This is to prevent the intermittent insomnia from perpetuating itself through conditioning and poor sleep hygiene to become persistent and more difficult to treat (Fig. 4 presents an algorithm).

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II The Primary Insomnias

5

Insomnia in Children and Adolescents

John Garcia

Insomnia affects youth from the cradle to college. Diagnosis and management of insomnia relies on an understanding of normal childhood sleep development. Using a developmental approach, this chapter describes insomnia in infants, toddlers, school-aged children, adolescents, and children with developmental disabilities. The treatment of insomnia in youth is driven by the diagnosis. Treatment, either behavioral or pharmacological, is described for each developmental group.

INSOMNIA IN THE INFANT AND TODDLER

The incidence of insomnia in the infant and toddler is 23–33% *(1-7)*. Understanding the importance of the internal biological clock or circadian rhythm is fundamental to the understanding of insomnia in the infant. Circadian rhythms refer to the intrinsic biological clock, which influences hundreds of physiological variables in humans. At birth, humans have a complete loss of all circadian rhythms *(8,9)*. There is a random distribution of sleep and wake throughout the 24-hour period. The newborn is essentially a blank slate relying on external cues or *zeitgebbers*, German for time-giver, to set the biological clock. The primary *zeitgebber* is light. With the appropriate influence of light, month 3 of life brings more consolidation of sleep with two-thirds of children having at least 5 hours of nocturnal sleep *(10)*. The classic pattern of nap in the morning, nap in the afternoon, and nocturnal sleep begins between 3 and 6 months of age *(11)*. By 6 months of age, the infant brain has the capacity to maintain 6 hours of consolidated sleep *(12,13)*. By approximately 18 months old, the toddler gives up the morning nap and transitions to a sleep pattern that usually includes one mid-day nap with the rest of sleep consolidated in the nocturnal hours.

Infants and toddlers may become fixed at an earlier developmental stage. For example, a 12-month-old may continue to wake several times a night. When a parent intervenes to help the child back to sleep, the opportunity for learning the necessary skill of putting oneself back to sleep is lost. The well-meaning parent may, among many behaviors, breastfeed, bottlefeed, or rock the child back to sleep. The child then associates the parent's behaviors with a return to sleep. This conditioned

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association is known as sleep-onset association disorder. The common marker in these behaviors is that they are not things that the infant can do for him or herself.

Treatment involves substituting an unacceptable association for an acceptable one and/or adapting the parent's response. For example, if a child demands a pacifier in order to sleep, parents may at first provide both the pacifier and a transitional object, such as a light blanket, that the child can get for him or herself. Then, the pacifier is provided as the second response for a while until it is finally forgotten. Gradual extinction has also been advocated by some researchers *(14)*. The emphasis here is on teaching the child self-calming skills and not "letting them cry it out." In this case, the child is put to bed drowsy but awake. Parents decide together how long to wait before intervening once the child begins to cry. Any amount of time is acceptable. If parents feel they can wait no longer than 20 seconds, they can begin there. When a parent enters the room, the goal is to help the child return to sleep as independently as possible. A transitional object may be offered. The child's back may be stroked for a brief time. Picking the child up, rocking, nursing or bottlefeeding until the child falls asleep must be avoided. Parents then increase the time they wait to intervene and decrease the time spent in the child's room as the child begins to learn self-calming skills. Consistency is important. The same plan is pursued during middle-of-the-night wakings. It is necessary for all caretakers to participate. Deviation by one caretaker can confuse the child and sabotage the learning opportunity. Generally, over several days to weeks, depending on the duration of the problem and the child's age, the child learns to go to and return to sleep independently.

Early treatment of children waking at night prevents symptoms from becoming a chronic problem. Conversely, studies have revealed that nocturnal waking that remains unaddressed after 17 months of age has an increased incidence of becoming a chronic disorder. Furthermore, children who continue to have persistent nocturnal wakings at 29 months have been found to have mothers who report feelings of being ineffective parents *(15)*.

Case 1

Amanda is a 2-year-old female with a history from both parents of "she wakes up several times a night screaming." Amanda was born 2 months premature and was sent home on an apnea monitor. Her parents were very vigilant during her first few months of life. They would often check to make sure she was breathing. Her apnea monitor was discontinued when she was 5 months old. Amanda's parents report that afterward, Amanda began having several nightly nocturnal arousals. The arousals would begin 90 minutes after Amanda's sleep onset and continue every 2 to 3 hours until she awoke for the day at 7 AM. Her parents often would bottlefeed and rock Amanda back to sleep. In fact, Amanda demanded the bottle and rocking in order to return to sleep after nocturnal arousals. There was no evidence of sleep-disordered breathing, reflux, or stereotypic movements.

The intervention in cases like Amanda's involves identifying the predisposing factors, explaining normal infant sleep physiology, and helping parents to do what they can. Amanda might be diagnosed with vulnerable child syndrome *(1)*. Amanda's history of prematurity caused her parents to perceive her as being vulnerable. With the best intentions, Amanda's parents became overly responsive to her normal arousals.

It is helpful to explain to parents that all children have brief arousals several times a night. Although these arousals are spontaneous, return to sleep can be hindered if parents intervene. Furthermore, Amanda's parents were gently reminded that at 2 years of age, Amanda was no longer at risk for Sudden Infant Death Syndrome.

The solution in cases like Amanda's is to gradually and gently decrease the amount of parental intervention. Additionally, in Amanda's case, the bedtime routine was changed. She was offered a cup of milk 1 hour before sleep onset. She was put to bed drowsy but still awake. When she cried out in the middle of the night, a parent would come to her bedside but would avoid picking her up, rocking her, turning on the light, talking to her, or providing things she could not get for herself such as the bottle. After several weeks of disciplined restraint by her parents, Amanda's behaviors during the night resolved.

Limit-setting sleep disorder is seen in children whose parents provide little or inconsistent bedtime routines. It is commonly seen in 2- to 6-year-olds. Bedtime struggles intensify with the child evading bedtime by stalling, whining, requesting snacks, and so on. This disorder ultimately leads to prolonged sleep-onset latency. Resolution occurs when parents communicate first with each other about a consistent bedtime practice and then implement this reliably with the child.

Differential diagnosis of the sleepless infant involves circadian issues, organic disorders, and parental stresses. Many children presenting with sleep-onset difficulties have a circadian rhythm that does not fit parental expectations. For example, a toddler with a biologically driven sleep-onset time of 9:30 PM is not going to adapt to a 7:30 PM bedtime no matter what behavioral modification tool is brought to bear. Using a sleep log (*see* Fig. 1) helps one to determine the child's intrinsic circadian rhythm.

There are several organic conditions seen in infants and toddlers that may interfere with initiating or maintaining sleep. Among the most common are reflux, milk-protein intolerance, and asthma. Reflux should be considered in infants who awaken fully and have difficulty returning to sleep *(16)*. Milk-protein intolerance can manifest as insomnia in infants. These children have elevated Immunoglobulin E levels and positive radioallergosorbent testing *(16)*. One study of infants averaging 4 months old with milk-protein intolerance identified frequent arousals (8–22 per night) and short sleep cycles that resolved when milk protein was eliminated from the diet *(17)*.

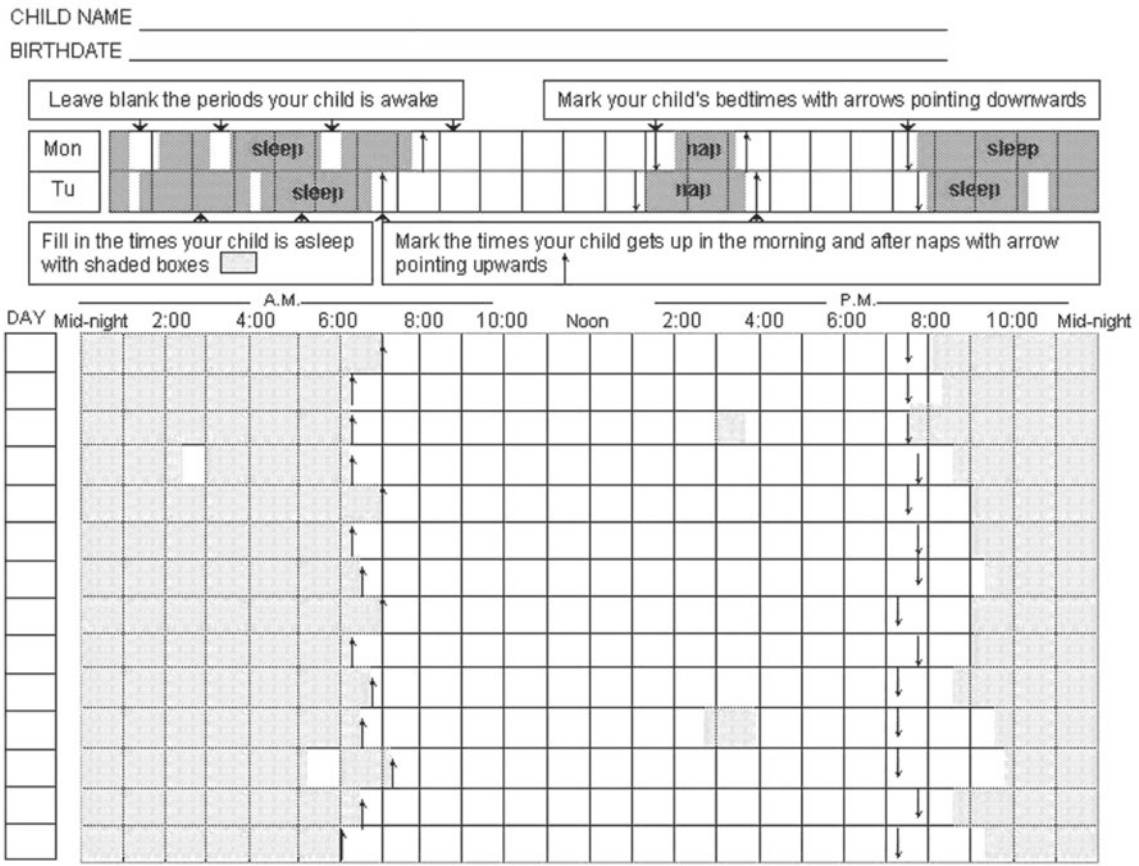

Fig. 1. A sleep log used in children.

Some children with asthma suffer from insomnia. Children with asthma have more frequent arousals and earlier final wake times *(18)*. Sleep-onset insomnia is rarely the problem. Most asthma attacks in children occur in the last two-thirds of the night *(19)*. This coincides with the poorest lung function occurring during the 24-hour cycle. Peak flow is 50% of waking maximum and oxygen saturations may fall 10% *(20,21)*. The nocturnal arousals associated with asthma have been found to have consequences for school performance. Increases in daytime sleepiness as measured using the epworth sleepiness scale, variable attention in school, and increased daydreaming as measured by neuropsychological tests. These tests measure both errors of commission that correlate with hyperactivity and omission that correlate with distractibility *(22)*.

Finally, although bruxism is not a cause of sleeplessness, it may be a symptom. Children who grind their teeth as a self-calming mechanism do so less when time in bed is decreased *(23)*.

INSOMNIA IN THE SCHOOL-AGED CHILD

School age includes the ages between 5 years and adolescence. The incidence of sleep disorders decreases in school-age children *(24)*. Fears and anxieties both at sleep onset and in the middle of the sleep period are the most common complaint in this age group. Often, these are short-term anxieties manifesting as insomnia. This is often termed adjustment sleep disorder. In other cases, anxieties may be a manifestation of more lasting emotional, psychological, or psychiatric disorders such as depression and posttraumatic stress disorder *(25)*. One must be aware that insomnia also may be a symptom of child sexual abuse *(26)*. Insomnia is commonly reported in children with attention deficit hyperactivity disorder (ADHD). Parents commonly report that these children have difficulty falling asleep, are restless sleepers, and awaken early *(27,28)*. Additionally, treatment for ADHD with stimulant medications may worsen sleep *(29)*.

SLEEP DISORDERS IN ADOLESCENCE

Adolescence sees the emergence of circadian rhythm disorders. Even teens without a circadian rhythm disorder have a tendency toward later sleep onset, increased total sleep requirement, and an increase in daytime sleepiness when compared to preadolescents *(30,31)*. Adolescents are predisposed to a delayed sleep onset. This is caused by a change in their biological clock. In reference to biological clocks, the term *period* refers to the length of the circadian cycle and is approximately, but not exactly, 24 hours. In the general population, the circadian period is approximately 24.5 hours, explaining why it is easier to stay up later than go to bed earlier for most people. In adolescence, the period becomes prolonged. In some teens, it may exceed 25 hours *(30,31)*. The biological phenomenon of delayed sleep phase driven by the adolescent circadian clock has been separated from the social pressures on teens to stay up later. Work by Carskadon et al. has emphasized that the tendency is biological and not merely a preference or effect of social pressures *(31)*. This emphasizes

the reality that the tendency toward delayed sleep-phase syndrome seen in teens is biologically driven by the circadian system.

The treatment of circadian rhythm disorders in children and adolescents can be discussed in three groups: chronotherapy, phototherapy, and pharmacotherapy. A review of the sleep log helps to set the context for discussion of chronotherapy or sleep–wake scheduling. A common method of chronotherapy is known as sleep-phase advancement *(32–34)*. Taking into account the youth's social expectations and requirements, a reasonable wake time is agreed upon. The agreed upon earlier wake time drives the sleep-onset time earlier. There is often a 3- to 5-day delay as the sleep phase advances. The teen may be advised that during this time, he or she may feel tired. It is emphasized that over the next 2 to 3 months, strict wake and bedtimes must be adhered to 7 days a week. Once a more appropriate sleep phase has been established, relaxing the schedule once or twice a week may be allowed if it does not throw the teen back into a delayed sleep phase. Alternatively, some physicians prefer to delay the sleep onset and wake time by several hours each day until the sleep-onset and wake times have been delayed to a phase consistent with the teen's social expectations. This form of chronotherapy is known as sleep-phase delay. For example, the teen falling asleep at 3 AM and waking at noon is asked to delay sleep onset until 6 AM. The wake time is proportionately delayed until 3 PM. On the second day, sleep onset is at 9 AM and wake time is at 6 PM. The sleep-onset time is delayed 3 hours each day until sleep onset is at 9 PM and wake time is at 6 AM. Thereafter, the sleep phase is fixed again for several months. One may choose to emphasize the nature of the relationship at this point. The physician is often seen as a coach. This places responsibility and control in the hands of adolescent.

Phototherapy is the second fundamental treatment in children with circadian rhythm disorders *(35–37)*. The goal is to decrease the evening light and increase exposure to waking bright light. It is important that the teen's exposure to bright light, including television and computer monitors is eliminated after 9 PM. In the morning, early morning bright light exposure with a light box or ambient light is effective in resetting the biological clock. Generally, 10,000 lux is necessary. Precautions should be taken to avoid exposure to ultraviolet spectrum *(38)* light. Use of light therapy should be avoided in patients with a history of bipolar disease as it can trigger mania. It should be emphasized that the patient need not look directly at thea light box; the direction of gaze may deviate 15°. It is recognized that children often have difficulty using a light box and integrating the light box into their morning routine is often a challenge. Some children choose to put the light box on the breakfast table or where they do their homework in the morning.

Medication therapy is mentioned last because it is rarely effective without simultaneously using sleep–wake scheduling and/or phototherapy. Two groups of medication have been described. The first is the sleep-inducing medications including the benzodiazepines and zolpidem. These medications are most effective when there is a pre-existing sleep debt. The second is melatonin. Melatonin has been shown to advance the sleep phase in some patients with delayed sleep-phase syndrome *(39–*

42). Melatonin must be taken approximately 3 to 4 hours before the desired sleep-onset time *(43)*. Many providers, including this author, are hesitant to use melatonin because it is not approved by the Food and Drug Administration. Additionally, it is a hormone. Possible effects during puberty have not been thoroughly studied.

Case 2

Josh is a 17-year-old male with a 5-year history of problems falling asleep. He is very clear that although he lies down in bed with the lights out at 11 PM most nights, he has difficulty falling asleep before 2 AM (*see* Fig. 2). On school days, he needs to be awakened at 6 AM. Waking him requires many calls and physical shaking. His first class begins at 7:15 AM. He admits to falling asleep daily in his first four classes. He feels that he becomes more alert after lunch. Once a week, he will take a 3- to 4-hour nap after school. On the weekends, he feels a sense of exhilaration and stays up until between 3 and 5 AM and awakens in the early afternoon. During summer vacation and holiday breaks, he follows a similar routine. He is quite motivated to improve his sleep–wake schedule. Family history reveals that Josh's mother also has a strong biological drive for late morning rising. In fact, she has chosen a job as a night-shift nurse accommodating her biological drive.

Intervention with Josh could be assigned to three categories: phototherapy, sleep–wake scheduling, and medication management. With regard to phototherapy, Josh agreed to use a light box on weekdays for 20 minutes after waking in the morning. It was emphasized that he did not need to stare directly at the light box. He could set it up so he was looking within 15° of his direct line of vision while he was finishing his homework in the morning, eating breakfast, or watching TV. On the weekends, he agreed to walk the family dogs in the morning upon waking, thus exposing his eyes to bright ambient light. Additionally, evening bright light exposure needed to be minimized. Exposure to television and computer screens after 9 PM was discouraged. Regarding sleep–wake scheduling, Josh agreed to awaken at 8 AM on weekends. Additionally, he agreed to minimize his afternoon naps. He was more amenable to this portion of the plan after it was explained to him that the drift toward later sleep onset and wake times on the weekends was sabotaging the progress he made during the week.

Many teens with delayed sleep-phase syndrome find that the early morning school start time is simply not compatible with their biological clock. In Josh's case, the biological underpinnings of his disorder were explained to school officials. The school adapted his schedule, allowing for a start time of 9 AM. Finally it was explained that medications are the least effective of the three management tools. Some people with the delayed sleep-phase syndrome who continue to have difficulty with sleep-onset insomnia despite all efforts, require changes in their external environment. This may mean considering evening school opportunities.

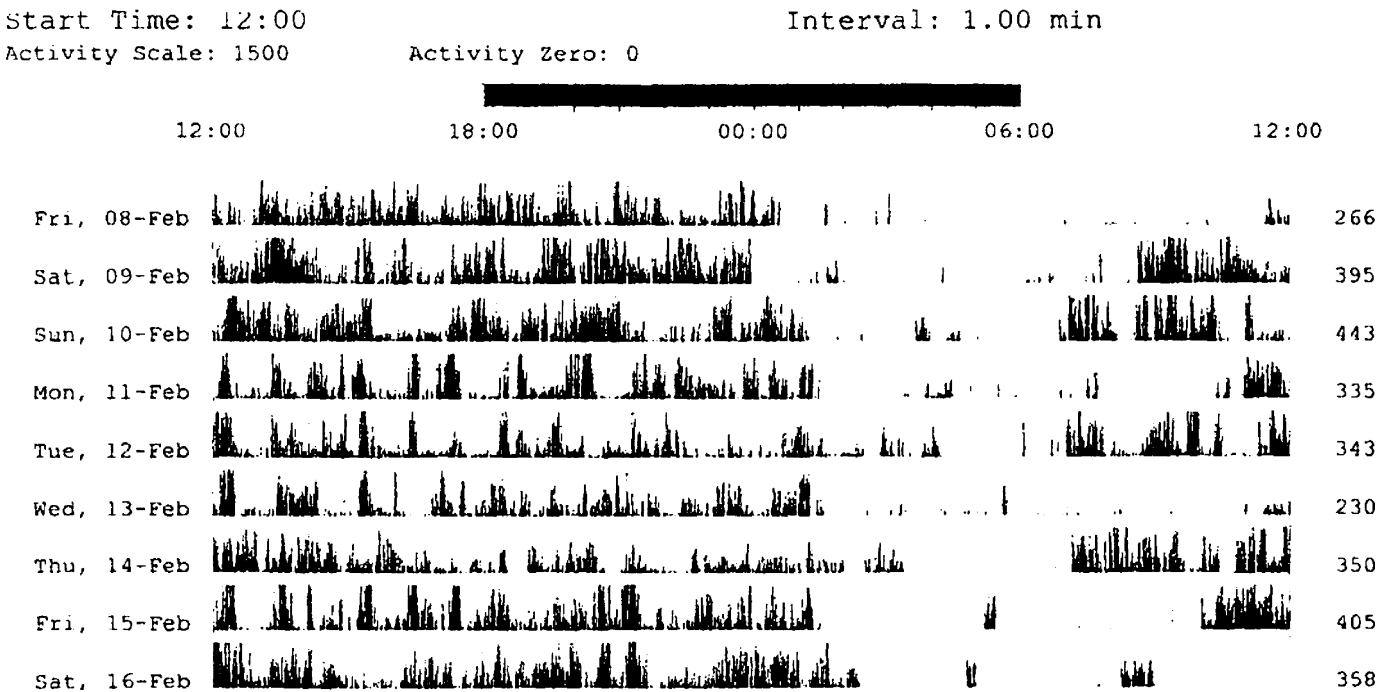

Fig. 2. Actigraph recording in a patient with delayed sleep syndrome (*see* Case 2).

INSOMNIA IN CHILDREN WITH DEVELOPMENTAL DISABILITIES

Insomnia is seen commonly in children with developmental disabilities *(44)*. One study of 214 children ages 1–18 with severe mental retardation found that 86% exhibited difficulties with sleep *(45)*. Sleep disorders in children with disabilities stress a sometimes already burdened family system. One study found that in children with disabilities without a sleep disorder, 21% of parents had daytime sleepiness. Of parents with children with disabilities and a sleep disorder, 64% of the parents complained of daytime sleepiness *(46)*.

Sleep disorders impact daytime behaviors in children with developmental disabilities. Irritability and mood lability are also increased *(47,48)*. The aberrant behavior checklist, used to quantify difficult behaviors in children with disabilities, was found to be increased when difficulties with sleep were identified *(49)*. There is an increase in self-injurious behavior in children found to have difficulties with sleep. Interestingly, worsening mental handicap does not predict increased incidence of sleep disorders.

Some syndromes are associated with an increased incidence of sleep difficulties including autism, Prader-Willi, Angelman, Smith-Magenis, Sanfilippo, Rett syndrome, and cerebral palsy. Of children with autism, 63–72% are identified as having sleep difficulties *(50–52)*. These problems are often severe. Sleep problems include prolonged sleep latencies (the length of time between going to bed and going to sleep), prolonged periods of nocturnal wakefulness, shortened total sleep time, and early morning waking. Children with autism are more likely to suffer from sleep disorders than other children with developmental delays, with the most common problem being early waking *(53)*. Of children with Sanfilippo syndrome, 78% have problems with sleep; 46% of which are severe enough to warrant medication management *(54)*. Of children with Smith-Magenis syndrome, 59% suffer from sleep problems *(55)*.

Treatment begins with the same basic principles used in children without developmental disabilities. For example, one study found that the gradual extinction technique described for sleep-onset association disorder resulted in quick and lasting reductions in sleep disorder symptoms in children with developmental disabilities *(56)*. Sleep–wake scheduling, or chronotherapy, has been found to be effective in children with developmental disabilities. In this case, the wake time is fixed. The nap time is minimized. Using a sleep log (*see* Fig. 1 for an example of a sleep log) the individual's average sleep requirement is determined.

The bedtime is then approximated and increased or decreased until a 90% sleep efficiency is achieved *(57)*. A combination of sleep–wake scheduling and phototherapy was effective in one study *(58)*. Finally, medication management is often required in this population. The benzodiazepines may not be effective in this population. *(59)*. Some authors have recommended choral hydrate *(60)*. Melatonin has been used effectively in a population of blind children with developmental disabilities *(59,61,62)*. Melatonin has been used in sleep disorders associated with

neurodevelopmental disabilities including Rett syndrome *(63)*, tuberous sclerosis, *(64)*, autism *(65)*, and Asperger syndrome *(51)*. Again, the reservations previously discussed in the treatment of circadian rhythm disorders apply here. Many sleep-inducing medications have been used, but in general, the literature is incomplete in measuring which medications are most effective. Further research is necessary.

Case 3

Erin is a 5-year-old girl with autism. Her sleep-onset time and wake times are variable. Her sleep-onset time ranges from 9 PM to 1 AM. Her wake time ranges from 4 AM to 9:30 AM. Additionally, she has difficulty maintaining her sleep. Several times a week she will be fully alert for 1 to 2 hours between 1 AM and 3 AM. Her daytime behavior deteriorates when she has nights of shorter total sleep time. She has no history of snoring. She takes a 1- to 2-hour afternoon nap when cared for by her grandmother 3 days a week.

Intervention for Erin involved sleep–wake scheduling and medication management. Her afternoon nap was gradually eliminated over a 3-week period. A regular wake time of 7 AM was initiated. Several weeks after the regular wake time was established, her middle-of-the-night arousals decreased to once every 2 or 3 weeks. It became clear that although most nights she was asleep by 10 PM, once or twice a week she continued to be awake after midnight. Her parents had already tried over-the-counter melatonin without much success. Doxepin (10 mg/1 mL) 2 mL (20 mg) was given when she was not asleep by 10:30 PM. This helped to further regularize her sleep phase.

CONCLUSIONS

A developmental approach to the diagnosis of youth with insomnia makes this difficult issue more approachable. Treatment is driven by the diagnosis. Careful patient- and family-specific treatments provide enormous benefits. Childhood treatment leads to the prevention of lifelong insomnia. Treatment of the child with a neurodevelopmental diagnosis provides relief to the family as well as the child.

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6
Psychophysiological Insomnia

Hrayr P. Attarian

O sleep! O gentle sleep! Nature's soft nurse, how have I frightened thee, That thou no more wilt weigh my eyelids down and steep my senses in forgetfulness?

—William Shakespeare (King Henry IV part 2 Act III Scene I)

DEFINITION

The *International Classification of Sleep Disorders* defines psychophysiological insomnia as "a disorder of somatized tension and learned sleep-preventing associations that results in a complaint of insomnia and associated decreased functioning during wakefulness" *(1)*. Psychophysiological insomnia is included under the category of primary insomnias in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) *(2)*. It is also commonly referred to as learned or conditioned insomnia and less commonly as functionally autonomous or internal arousal insomnia.

HISTORICAL PERSPECTIVES

The suspicion that maladaptive learning coupled with poor sleep hygiene can cause insomnia was first mentioned in landmark publications by Betollo in 1931 *(3)* and Strauss in 1948 *(4)*. The diagnostic category of persistent psychophysiological insomnia was first created in the 1979 *Diagnostic Classification of Sleep and Arousal Disorders* published by the Association of Sleep Disorders Centers. It was defined as "insomnia that develops as a result of the mutually reinforcing factors of chronic, somatized tension anxiety and negative conditioning to sleep" *(5)*. In 1983, Peter Hauri published a paper showing that a cluster analysis could identify psychophysiological insomnia on the basis of polysomnographic variables, psychological questionnaires such as the Minnesota Multiphasic Personality Inventory (MMPI), and a sleep history *(6)*. In another seminal study, Hauri and Fisher compared psychophysiological insomniacs, normal sleepers, and insomniacs with dysthymic disorder. The two insomnia groups (psychophysiological and dysthymic)

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showed similar degrees of sleep impairment. Psychologically, however, patients with persistent psychophysiological insomnia were similar to normal sleepers and different from dysthymic patients, except that psychophysiological patients were more likely to be repressors or sensation avoiders than normal subjects. Additionally, psychophysiological patients suffered more than either normal subjects or dysthymics from tension-related symptoms such as muscle tension headaches *(7)*.

EPIDEMIOLOGY

The exact incidence and prevalence of psychophysiological insomnia is unknown. In a study of 216 patients with insomnia from five centers, psychophysiological insomnia was the primary diagnosis in 12.5% of all cases and a secondary diagnosis in another 27.2% *(8)*. A different study found that of 113 subjects complaining of insomnia, 11.3% had psychophysiological insomnia *(9)*. According to a third study of 8000 patients seeking help for insomnia at multiple sleep centers, about 15% were diagnosed with psychophysiological insomnia *(10)*. Psychophysiological insomnia is often diagnosed as a secondary problem because learned associations often prevent or disrupt sleep in many other forms of chronic insomnia.

ETIOLOGY

A few nights of disturbed sleep due to stress such as psychological distress, physical pain, or any other acute internal or external event, is a universal human experience. In other words, anyone can have a few bad nights of sleep. In the majority of cases, the trouble is short-lived. People suffering from psychophysiological insomnia, however, continue to have poor sleep despite the resolution of the acute event. In the development of pyschophysiological insomnia there are three factors playing a role:

1. Predisposition: being an excessive worrier *(11)*, being physiologically hyperaroused *(12)*, and familial inheritance of the tendency to develop insomnia *(13)*.
2. Precipitant: a transient stressor.
3. Perpetuating factors: the individual's expectation of a poor night's sleep that becomes a self-fulfilling prophecy and the counterproductive trials to sleep *(11)*.

In some patients with psychophysiological insomnia, either a precipitant is not found or the stressor is so minor that it has been forgotten. Rather, poor sleep may have gradually developed as an occasionally occurring disturbed night leads to increased concern, causing sleep to deteriorate in a snowball fashion, until it becomes the patient's chief concern *(12)*.

PATHOGENESIS AND PATHOPHYSIOLOGY

The role of organic components in the pathophysiology of insomnia is well documented. There is growing evidence that shows the biological basis of psychophysiological insomnia to be moderate physiological hyperarousal or an imbalance of the sleep–wake system toward alertness. Physiological hyperarousal is documented in many other types of primary insomnia as well *(14,15)*.

Insomniacs display faster heart rates *(16)*, higher 24-hour metabolic rates *(14)*, higher body temperatures *(17)*, and higher resting electromyogram activities (leading to an inability to relax) *(18)*. They are also as or more alert than controls during the day; their Multiple Sleep Latency Tests show increased sleep latency (SL) as compared to controls *(19)*. By electroencephalography (EEG) criteria, insomniacs tend to have a higher percentage of faster frequencies both in waking and in sleeping *(18,20)*. Lamarche and Ogilvie compared patients with psychophysiological insomnia to patients with psychiatric insomnia and to normal controls. EEG activity showed higher cortical arousal in the psychophysiological insomniacs vs the other two groups, which did not differ from each other significantly. Psychophysiological insomniacs had less α during the first part of the sleep-onset period and did not show the dramatic drop in α across the sleep-onset period that characterizes normal sleep *(21)*. Vgontzas and colleagues discovered a positive correlation between objective sleep disturbance and the activity of both limbs of the stress system (the hypothalamic–pituitary–adrenal axis and the sympathetic system) and increased serum levels of adrenocorticotropic hormone and cortisol in a group of chronic insomniacs *(22)*.

CLINICAL MANIFESTATIONS

Patients with psychophysiological insomnia usually give a history of being light sleepers even before the development of persistent difficulty initiating or maintaining sleep.

Patients suffering from psychophysiological insomnia focus attention on inability to sleep. The insomnia becomes the only perceived source of distress. Other emotional or mental concerns are either minimized or are absent. Stress factors involved in the development of the insomnia are either forgotten or patients typically deny awareness of these factors, unable to find any reason for the insomnia *(12)*.

Psychophysiological insomnia is typically acquired during a period when other factors, such as stress, can cause insomnia. After a few days of sleeping poorly, the patient becomes concerned about his or her inability to sleep, trying harder to get to sleep, which causes arousal and aggravates the insomnia. The stimuli surrounding the bedtime event (such as the bed itself, the bedroom, etc.) may become conditioned triggers to arousal *(12)*. Thus, such patients may have severe problems sleeping in their own bedrooms but often sleep remarkably well in other situations, such as on the living room couch, in a motel, or in a laboratory.

The sleep disturbance in persistent psychophysiological insomnia ranges from mild to severe. Characteristically, the polysomnogram (PSG) reveals increased SL, increased percentage of stage 1 sleep, and increased number of brief arousals; otherwise the sleep architecture is within normal limits *(23)*. However, these features are simply the hallmarks of poor sleep in general and they are not specifically diagnostic of psychophysiological insomnia.

Maladaptive behaviors also contribute to the development of the psychophysiological insomnia. Common maladaptive behaviors include laying awake in bed for hours on end trying to go to sleep, which of course increases frustration and

agitation and hence the arousal and aggravates the insomnia; watching the clock and counting the hours left before one has to get up; sleeping in in the mornings in order to "catch up"; doing housework, homework, or office work while awake at night; and, in rare cases, napping during the day. All these behaviors are engaged in "in good faith" but tend to exacerbate the problem rather than alleviate it.

A deterioration of mood and motivation as well as problems with attention, vigilance, and concentration are associated with psychophysiological insomnia *(1)*. Studies have shown that these symptoms are secondary to central nervous system arousal and not to poor sleep *per se (24)*.

Of note, patients with psychophysiological insomnia complain bitterly of fatigue and difficulty with concentration and attention but almost never give a history of falling asleep unintentionally during the day. Only rarely are they able to even nap in the daytime.

Within the limits of a normal personality profile, patients with psychophysiological insomnia tend to be more tense, generally less satisfied, and are typically emotional repressors and deny problems *(12, 25)*. There usually is a positive family history of insomnia and/or light sleepers.

Acute physical and psychological stressors tend to exacerbate insomnia, as does shift work *(26)*. Pregnancy may aggravate psychophysiological insomnia as well, especially in the first and third trimester *(27)*.

According to the *ICSD*, the following criteria must be satisfied to diagnose psychophysiological insomnia: (1) a complaint of insomnia and a complaint of decreased functioning during wakefulness; (2) indications of learned, sleep-preventing associations, such as trying too hard to sleep or showing conditioned arousal to the bedroom; (3) evidence for increased somatized tension, such as agitation, high muscle tension as manifest in tension headaches, or increased sympathetic tone; (4) the PSG, if used, shows disturbed sleep; (5) no other medical or psychiatric disorder can account for the severity of the sleep disturbance, although most patients with psychophysiological insomnia are somewhat anxious and dysphoric; and (6) other sleep disorders may co-exist with the insomnia (e.g., poor sleep hygiene and obstructive sleep apnea [OSA]) *(1)*.

Case 1

K is a 41-year-old woman who presented to the sleep center outpatient clinic for initial evaluation of a year's history of sleep-onset and sleep maintenance insomnia. K was always a light sleeper, but about 1 year ago, after the death of her mother, she started having trouble falling and staying asleep. Prescription sleep aids help her go to sleep within a reasonable time, but she wakes up at 4 AM unable to return to sleep.

She has tried napping during the day, but cannot. She does not fall asleep unintentionally, although she feels fatigued during the day. At night when she is awake, she tosses and turns in bed and never leaves the bed or the bedroom. Currently, she is between jobs, so in the morning when she wakes

up around 4:30–5 AM she stays in bed, dozing on and off until about 11 AM. Prior to this, she used to go to bed around 10–11 PM, fall asleep within an hour or so, and then wake up at 4 AM and stay in bed tossing and turning until about 7 AM when she had to get up to go to work. She tried drinking alcohol just before bedtime to help her fall asleep. She does not use caffeine during the day. She denies snoring, observed apneas, cataplexy, sleep paralysis, hypnagogic hallucinations, and choking spells. She denies waking up gasping for air. She denies symptoms of restless legs.

DIFFERENTIAL DIAGNOSIS

Psychophysiological insomnia lies on a continuum with a number of other diagnostic categories.

Idiopathic insomnia is diagnosed if the predisposition toward poor sleep by itself is severe enough to cause insomnia. Psychophysiological insomnia is assumed to start with a somewhat milder predisposition toward poor sleep that usually develops into insomnia only with the occurrence of some other, identifiable stressor acting as the trigger *(1)*.

A sleep state misperception (SSM) is when the patient sleeps adequately but does not perceive it as sleep *(28)*. In this disorder, complaints of insomnia occur without any objective evidence of sleep disturbance. Patients may report that they have not slept at all in weeks, months, or years. However, on objective sleep studies, they sleep several hours per night. When results of sleep evaluation are presented, patients with SSM may vehemently insist that the studies are in error because they are convinced that they sleep very little, if at all.

Idiopathic, or childhood-onset, insomnia is a rare condition presenting as a chronic, serious inability to initiate and maintain sleep, which can often be traced back to the first few weeks of life.

Circadian rhythm abnormalities occur when the patient sleeps well but not at socially acceptable times *(28)*. Those with the advanced sleep-phase syndrome have excessive sleepiness in the evening and undesired early morning awakening. Those with the delayed sleep-phase syndrome have sleep-onset insomnia, excessive daytime sleepiness (particularly in the morning), or both.

Inadequate sleep hygiene is the diagnosis when insomnia is maintained primarily by neglecting sleep hygiene and engaging in behaviors that are not conducive for sleep (e.g., drinking too much coffee, exercising too close to bedtime, napping, staying in bed too long, drinking alcohol too close to bedtime). To the extent that the insomnia is independent of the precipitating causes and also independent of the quality of sleep hygiene, psychophysiological insomnia is the preferred diagnosis *(28)*.

Generalized anxiety disorder is the preferred diagnosis when anxiety permeates most aspects of a patient's functioning (anxiety in social interactions, about job performance, etc.). Psychophysiological insomnia is preferred when the anxiety is focused almost exclusively on poor sleep and its consequences on daytime functioning *(28)*.

Affective disorder is sometimes difficult to separate from psychophysiological insomnia because a dysphoric mood that is ascribed to the effects of poor sleep often accompanies psychophysiological insomnia. It is especially difficult to distinguish dysthymia from psychophysiological insomnia in cases of "masked" depression (i.e., when the patient denies overt sadness or hopelessness). Often, the discrimination can be made on other "vegetative signs," such as loss of appetite or libido or the typical diurnal fluctuation of depression (morning being worse). In the final analysis, the diagnostician's sense is important whether depression is still driving the insomnia, or whether the insomnia is driven by maladaptive sleep habits learned during a previous depression. Also, dysthymic patients may typically show depressive traits before the insomnia developed *(1)*.

In general, a diagnosis of psychophysiological insomnia should not be made if the patient fulfills criteria for any other Axis I or II diagnosis in the *DSM-IV (2)*.

Medical causes of insomnia include propriospinal myoclonus *(29)*; restless legs syndrome, which is a common condition characterized by a desire to move the legs; accompanying paresthesias that are characterized as uncomfortable or indescribable that interfere with sleep; cardiorespiratory disorders; pain; degenerative disorders; prostatic hypertrophy *(30)*; OSA disorder *(31,32)*; and HIV infection *(33)*.

Medications, recreational drugs, and toxins can also cause insomnia and a full list of medications, ingested substances, and chemical exposures should be obtained. Among medications causing insomnia, the most common are stimulants, theophylline, prednisone, and selective serotonin reuptake inhibitors. Withdrawal from sedative medication can also cause insomnia in addition to idiosyncratic reactions to other medications such as the anticonvulsants, felbamate *(34)* and lamotrigine *(35)*. Substances such as alcohol or other recreational drugs can cause insomnia *(10)*, as can environmental toxins such as carbon monoxide or inorganic mercury *(36,37)*.

MENOPAUSE-RELATED INSOMNIA

There is a high level of sleep disturbance occurring in about 42% of middle-aged women *(38)*. Although cross-sectional analyses indicate that sleep disturbance may be independent of menopausal status, transition into postmenopausal status is associated with deleterious changes in sleep among women not receiving hormone replacement therapy *(38,39)*.

The prion diseases of Creutzfeld Jacob and Fatal Familial Insomnia can be extremely rare causes of insomnia. More commonly, Alzheimer's disease, Parkinson's disease, and other degenerative neurologic conditions can have prominent symptoms of insomnia. Rarely, brain stem lesions can also produce insomnia *(40)*.

DIAGNOSTIC WORKUP

The diagnosis of psychophysiological insomnia is typically and often made by history and observation. Eliciting an account of learned associations preventing sleep and paying attention to the patient's display of somatized tension are key in making the diagnosis. To rule out other causes one needs to perform the following:

1. A brief psychiatric interview specifically looking for neurovegetative symptoms of affective disorders and/or anxiety permeating daily activities other than sleep. Occasionally, psychological tests such as the MMPI and Profile of Mood States are used, looking for a profile of malaise, guardedness, sensation avoidance, repression, and denial. (The abnormalities on the psychological tests may be either the cause or the result of insomnia.)
2. A general medical evaluation to rule out physical problems, such as other medical or neurologic disorders, medication effects, or substance abuse *(10)*.
3. According to the American Academy of Sleep Medicine practice parameters, polysomnography is not indicated in the routine evaluation of insomnia, except when another sleep disorder is suspected and when insomnia does not respond to appropriate treatment.
4. A sleep log is a graph on which, for 2 to 3 weeks, the patient records bedtime, approximate sleep time, times and duration of awakenings during the sleep period, final awakening time, and naps taken during the day. This record summarizes the patient's perception of the amount and quality of sleep he or she is getting.
5. Actigraphy is an invaluable tool for evaluating insomnia, especially in patients with unusual complaints, such as "I don't sleep at all." It supplements subjective sleep logs. An actigraph is a small, wrist-mounted device that records the activity plotted against time, usually 1 or 2 weeks at a time. There is a close correlation between the rest activity recorded by the actigraph and the wake–sleep pattern as determined by the PSG *(41)*. Certain standardized questionnaires are sometimes used to screen for insomnia and determine its severity *(42,43)*.

PREVENTION

In early and aggressive treatment of transient insomnia, both with hypnotics and a discussion of good sleep hygiene, addressing the acute stressor may prevent the development of the learned maladaptive associations leading to psychophysiological insomnia *(11)*.

PROGNOSIS AND COMPLICATIONS

If untreated, psychophysiological insomnia can continue for decades. In some cases, it gradually worsens as a vicious cycle of insomnia develops. Overall quality of life, as measured by the SF-36 Health Status Survey, is greatly impaired by chronic insomnia *(44)*. Complications, as in any serious insomnia, include excessive use of hypnotics, self-treatment with alcohol, treatment of ensuing daytime somnolence by stimulants, and daytime tension with tranquilizers *(45)*. Untreated insomnia is a risk factor for the subsequent development of clinical depression and psychiatric distress *(30,46)*. Other psychological complications include a passive and defeatist attitude *(1)* and cognitive, particularly memory, impairment *(47,48)*. Chronic insomnia is also associated with an increase in motor vehicle accidents and a decrease in job performance *(49)*.

MANAGEMENT

There are two main categories of treatment modalities for psychophysiological insomnia: behavioral and pharmacological. The best management strategy is combining hypnotic medication and behavioral methods *(50)*. Although current Food

and Drug Administration guidelines recommend hypnotic medication only for short-term use, studies have shown that the risk of tolerance, addiction, dependence, and rebound insomnia are minimal *(51–53)*. Hypnotics that have clinically proven efficacy include the newer nonbenzodiazepine hypnotics, zolpidem *(54,55)*, zopiclone *(56)* (not available in the United States), and zaleplon *(57,58)*; the benzodiazepines; and low-dose trazodone. Two studies have shown efficacy of valerian root in the treatment of insomnia, comparable, according to one of the studies, to that of oxazepam (a benzodiazepine) *(59,60)*. Tricyclic antidepressants and antihistamines (including over-the-counter [OTC] sleep aids) are rarely indicated because of a poor side-effect profile and unproven value as hypnotics. There is paucity of data on the efficacy of antidepressants and OTC sleep aids in the treatment of insomnia. Additionally, the risk of serious adverse effects with these medications is well documented *(52,61)*. There is also growing evidence that the benefits of benzodiazepine treatment outweighs the risks in the vast majority of patients. Despite these facts, there has been a significant increase over the past several years in the use of antidepressants and OTC sleep aids in the treatment of insomnia with a concomitant decrease in the use of hypnotics *(52)*. A recent study showed that long-term use of zolpidem is safe, well-tolerated, and effective in the treatment of chronic insomnia *(62)*.

Behavioral methods include sleep restriction consolidation, sleep hygiene education, relaxation therapy, and stimulus control therapy *(63,64)*. These behavioral methods are effective in increasing the total sleep time by 13%, reducing SL by 65%, and reducing the wake time after sleep by 48% *(65–67)*.

Case 2

A 42-year-old woman referred with the chief complaint of sleep maintenance for approximately 10 years. She is able to initiate sleep, but, a few hours later she wakes up and is unable to return to sleep. Typically, she wakes up in the middle of the night to go to the bathroom, and then is wide awake. She is awake for several hours and lays in bed trying to go back to sleep but tends to worry about issues relating to work, home, and family. Occasionally, she sleeps for brief periods of time throughout the rest of the night. This problem has gradually been worsening over a 10-year period. She stopped drinking caffeine approximately 2–3 years ago, which helped slightly, but did not have a significant impact. She had been taking Tylenol PM for a year or so approximately 4 years ago, which initially helped, but after a while the medication stopped helping her sleep through the night. She has tried not taking Tylenol PM and she said her insomnia became much worse. She most recently has been taking temazepam about once or twice a week when she feels particularly anxious and fears that she will not be able to fall asleep at all. She says this is quite effective and she tends to sleep through most of the night.

Although this has been going on for some time, she has just recently sought medical attention because of her recent problems with fatigue and a difficulty

Sleep Log

Clinical Vignette
Ms. S. prior to treatment

Name _____ Weeks of _____

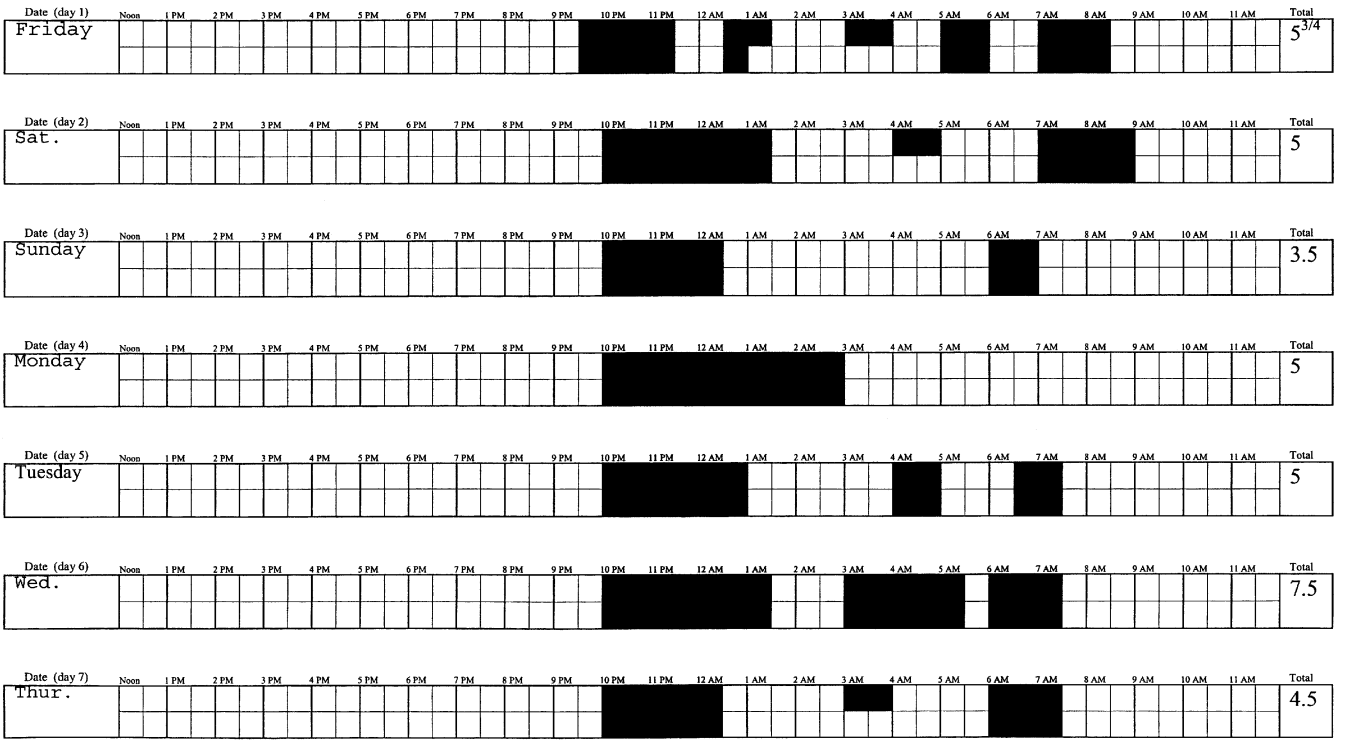

Fig. 1. Sleep log prior to treatment.

Sleep Log

Clinical Vignette
Ms. S after treatment

Name _____ Weeks of _____

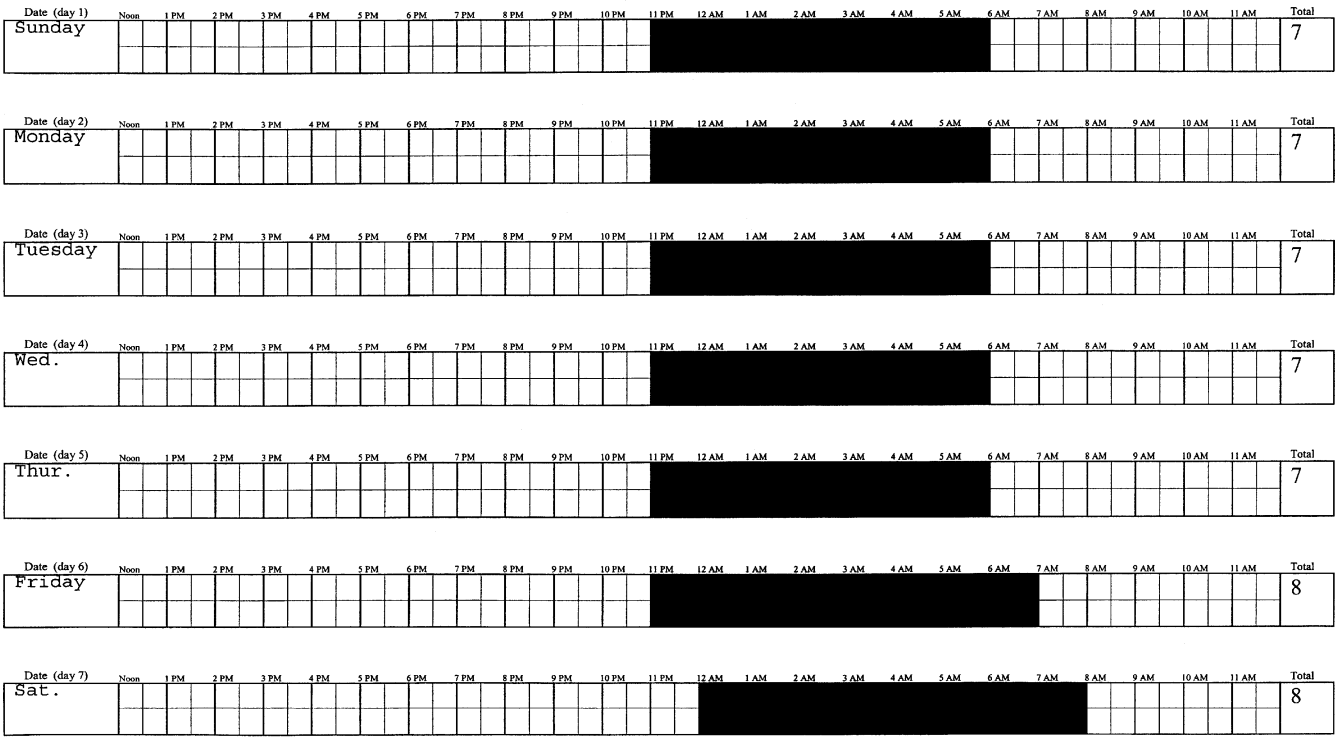

Fig. 2. Sleep log after treatment.

concentrating. Overall, during the day she feels fatigued, but does not nap and does not fall asleep unintentionally during the day. She states that she has been a light sleeper for most of her life but cannot remember a particular event that triggered the insomnia 10 years earlier. She has a positive family history of insomnia in two siblings.

She was asked to keep sleep diaries for two weeks and bring them in during her followup visit. (Figure 1 reproduces one of those logs.)

She was placed on a nightly dose of temazepam and also on a sleep restriction consolidation program restricting her time in bed to 5 hours. She was also asked to continue keeping sleep logs and fax them in every 3 weeks, at which point her time in bed would be adjusted according to her overall sleep efficiency.

Six months after she was averaging 7–8 hours of sleep at night, she was gradually tapered off the temazepam. Figure 2 illustrates one of her last sleep logs after the discontinuation of the temazepam.

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7
Idiopathic Insomnia

Hrayr P. Attarian

You know I can't sleep, I can't stop my brain

You know it's three weeks, I'm going insane.

You know I'd give you everything I've got for a little peace of mind.

—The Beatles (I'm so tired)

DEFINITION

The *International Classification of Sleep Disorders* (*ICSD*) defines idiopathic insomnia, or childhood-onset, insomnia as a lifelong inability to get adequate amounts of sleep.

This is presumably due to an abnormality in the neurological control of the sleep–wake system *(1)*. However, not everyone agrees that this disorder is a separate and unique type of insomnia. For example, the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV)* regards the apparent neurological predisposition toward insomnia described here as a component of a broader entity named *primary insomnia* that includes idiopathic insomnia, psychophysiological insomnia, and sleep state misperception (SSM) *(2,3)*.

HISTORICAL NOTE

The Association of Sleep Disorders Centers (now the American Academy of Sleep Disorders) developed and published *Sleep Nosology* in 1979. In that publication, a new category entitled "childhood-onset insomnia" was presented. It was described as "sleep-onset and sleep maintenance insomnia, resulting in daytime symptoms of inadequate sleep, that is characterized by a distinctive history of (unexplained) development before puberty, and persistence into adulthood." It was postulated that this new entity represented "a CNS [central nervous system] shift or dysfunction of the sleep-arousal equilibrium" *(4)*. The existence of this disorder

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was confirmed by research done in the 1980s. It was also documented that this is a distinct form of insomnia by showing that childhood-onset insomnia was different from adult-onset insomnia on polysomnographic grounds *(5)* and that it could be distinguished from other types of insomnia in a cluster analysis *(6)*.

EPIDEMIOLOGY

Idiopathic insomnia is rarely seen in its pure form. Chronic and serious insomnia over a lifetime almost always leads to other factors such as maladaptive behaviors; poor sleep hygiene, and emotional disturbances that further complicate the picture *(7)*. A predisposition toward poor sleep exists in many insomniacs. However, in its pure form, idiopathic insomnia represents less than 5% of all insomniacs *(8)*. Evidence shows that idiopathic insomnia often, but not always, has familial patterns of inheritance *(1)*.

ETIOLOGY

Idiopathic insomnia may be due to some dysfunction in the brain's sleep–wake center. It may represent either hyperactivity in the wake center or hypoactivity in the sleep center *(5,9)*. Another, and more commonly accepted theory, is that patients with idiopathic insomnia are just simply organically hyperaroused *(10)*.

PATHOGENESIS AND PATHOPHYSIOLOGY

Sleep–wake centers include the sleep-promoting center present in the anterior hypothalamus, the raphe nuclei, and medial forebrain area, and the wake-promoting center in the ascending reticular-activating system including the posterior hypothalamus *(7,9)*. Whether a person is awake or asleep depends on the neurophysiological balance between the reticular-activating system and the sleep-inducing maintenance systems *(11)*. Idiopathic insomnia presumably is due to a shift of this balance toward arousal. Either hyperactivity in the arousal system or hypoactivity in the sleep system may cause idiopathic insomnia *(9)*. Patients suffering from idiopathic insomnia may have a neurochemical, neuroanatomical, or neurophysiological dysfunction or lesions interfering with normal sleep *(11)*. Idiopathic insomniacs are often hyperaroused during wakefulness on questionnaires, auditory-evoked potentials, and electroencephalogram (EEG) *(12)*. Physiological hyperarousal in many systems (cardiac, core temperature, corticosteroids, etc.) is not confined to patients with idiopathic insomnia but is frequently found in all primary insomniacs *(10)*. Despite animal data showing the creation of insomniac animals with medial forebrain and the medial preoptic area *(13)*, no direct human evidence for structural neuropathology exists *(14)*. Difficult birth and prematurity are likely risk factors for the development of idiopathic insomnia *(1)*.

CLINICAL MANIFESTATIONS

Idiopathic insomnia is a chronic and serious inability to initiate and maintain sleep that can often be observed as early as the first few weeks of life. Parents often

report that these patients slept much less, or required less sleep, than their siblings when they were infants. Sleep latency is long. Sleep is riddled with many awakenings and may show sleep-stage abnormalities, such as rapid eye movement (REM) sleep with few eye movements or ill-formed sleep spindles during stage 2 sleep *(5)*. Paradoxically, idiopathic insomniacs may show fewer body movements per unit of sleep than do normal sleepers *(14)*. The spectrum of severity of insomnia in this condition varies from mild (essentially a light sleeper) to severe and incapacitating, as the presumed underlying neurological abnormality varies from mild to severe *(14)*. Daytime features typically include decreased attention and vigilance, low levels of energy and concentration, and a deterioration of mood commonly described as grim and subdued, rather than obviously depressed or anxious. In mild or moderate idiopathic insomnia, psychological functioning is remarkably intact. In severe cases, daytime functioning may be severely disrupted and affected patients may be unable to hold a job. During childhood and adolescence, idiopathic insomnia is often associated with soft neurological signs (i.e., as dyslexia or hyperactivity). Many cases show diffuse nonspecific abnormalities on the EEG *(1)*.

The ICSD's diagnostic criteria for idiopathic insomnia are (1) a complaint of insomnia combined with a complaint of decreased functioning during wakefulness; (2) long-standing insomnia, typically beginning in early childhood or soon after birth; (3) relentless insomnia during periods of both poor and good emotional adjustment; (4) one or more of the following polysomnography: increased sleep latency, reduced sleep efficiency, and increased number and duration of awakenings often a reversed first-night effect (best sleep on the first night); (5) the diagnosis cannot be made if medical or psychiatric disease or stress can explain the early

Case 1

Mr. T. is a 53-year-old man with lifelong history of insomnia. Mr. T. stated that his mother told him that he had trouble sleeping even during his infancy. He stated that as far back as he could remember he has had insomnia. Around age 10 or 11 he started having some anxiety associated with his inability to sleep. He stated that when he has a decent night's sleep for several nights in a row, he really does not feel depressed and anxious; but not getting a good night's sleep creates anxiety over the inability to sleep, which then becomes reinforced when he does not sleep easily the following night.

For reasons unknown, he did not seek medical attention for his problem until about 1 year ago when he mentioned it to his primary care physician. He was tried on Xanax, Ambien, Trazodone, Remeron, and over-the-counter Tylenol PM. Few medications had any impact on his sleep. Even with medication, he had only one good night every 2–3 weeks, during which he would sleep 6–7 solid hours.

Most of the time, Mr. T. goes to bed between 11 PM and midnight feeling sleepy and tired, but when he lays down he is awake for at least 1 hour, some-

times worrying about the day's events or sometimes just laying there. He then manages to fall asleep, only to wake up several times in the middle of the night, staying awake each time for 30–40 minutes. His total awake time in the middle of the night, he reports, is about 2 hours. He wakes up between 8 and 8:30 AM feeling fatigued and not restored. Despite his fatigue, he is not sleepy during the day, does not fall asleep unintentionally, and does not take naps. He has no other sleep complaints, and he does not have any family history of insomnia. Physical exam is normal.

onset of this insomnia; and (6) other sleep disorders causing insomnia can occur simultaneously (e.g., adjustment sleep disorder). Minimal criteria: 1, 2, and 5 *(1)*.

DIFFERENTIAL DIAGNOSIS

Not all insomnia in childhood is idiopathic or childhood-onset insomnia. Although the complaints of insomnia are seen in up to 41% of children *(15)*, as mentioned previously, idiopathic insomnia in its pure form is rarely seen. Idiopathic insomnia is diagnosed when insomnia predates the development of the other complicating factors (emotional problems, ill adaptive associations, or poor sleep hygiene) and when the imbalance of the sleep–wake system plays a paramount role *(1)*.

Idiopathic insomnia should be differentiated from other common childhood insomnias such as sleep-onset association disorder and limit-setting sleep disorder. In the former, habits, objects, or conditions become associated with the transition to sleep and need to be re-established throughout the night to permit return to sleep after normal awakenings, otherwise periods of waking are prolonged *(16)*. The latter is a disorder of childhood characterized by normal sleep ability and deliberate attempts to remain awake at bedtime and, sometimes, after nighttime awakenings using a variety of requests, demands, and stalling tactics (stories, drinks, bathroom trips, blanket adjustments, television) *(16)*. A careful history of the child's bedtime behavior enables one to distinguish these disorders from idiopathic insomnia.

Idiopathic insomnia is differentiated from short sleepers by the accompanying fatigue and daytime performance impairment, whereas short sleepers feel and function well during waking hours.

Idiopathic insomnia is difficult to distinguish from psychophysiological insomnia, which is also accompanied by an innate predisposition toward poor sleep. In idiopathic insomnia, the presumed sleep–wake imbalance is enough to cause the insomnia by itself; in psychophysiological insomnia, the inherent sleep–wake disturbance is weaker, needing the addition of the stress of maladaptive conditioning to trigger the insomnia *(1)*.

Psychologically, most patients with idiopathic insomnia are remarkably healthy, given their chronic lack of sleep *(1)*. However, as in other primary insomnias, patients with idiopathic insomnia tend to be emotional repressors *(7)*. Although the insomnia is persistent, relentless, and almost unvaried through both poor and good

periods of emotional adaptation *(1)*, patients do experience occasional worsening of their sleep under stressful situations *(7)*.

DIAGNOSTIC WORKUP

Idiopathic insomnia is a diagnosis of exclusion. A careful history identifies the exact onset of the insomnia and is important in defining any maladaptive behaviors, sleep hygiene issues, and extrinsic factors. A thorough psychiatric interview reveals no psychological reason severe enough to explain the insomnia. Specifically, no psychological distress explains the early onset. A general medical evaluation reveals no causative medical factors such as allergies, pain, or thyroid abnormalities that might have been operative since early childhood. A polysomnogram (PSG), if performed, reveals severely impaired sleep, and sleep stages may be difficult to score according to accepted criteria. However, because idiopathic insomniacs often show a "reverse first night effect" *(6)*, more than one night in the sleep laboratory may be necessary. Another way of bypassing the reverse first night effect is doing actigraphy. Actigraphy is an invaluable tool in evaluating insomnia, especially in patients with unusual complaints, such as "I don't sleep at all." It supplements subjective sleep logs. An actigraph is a small wrist-mounted device that records the activity plotted against time, usually 1 or 2 weeks at a time. A close correlation exists between the rest activity recorded by the actigraph and the wake–sleep pattern as determined by the PSG *(17)*. Nonspecific EEG abnormalities may be seen, but are highly idiosyncratic and are not diagnostic of idiopathic insomnia. Overall, PSGs add little of diagnostic value in idiopathic insomnia.

PROGNOSIS AND COMPLICATIONS

The suspected neurological abnormality underlying the idiopathic insomnia is presumably lifelong. Therefore, the symptom of insomnia to a certain degree persists for the person's entire life. Complications, like with other primary insomnias, include depression *(18)*, attempts to treat the condition either by self-medication (such as with alcohol) or by prescriptions (high doses of benzodiazepines or barbiturates), excessive use of stimulants to promote alertness *(1)*, and, as mentioned previously, the development of maladaptive behaviors and poor sleep hygiene.

MANAGEMENT

No guidelines for a consistent treatment approach to childhood-onset insomnia are available. Impeccable sleep hygiene is essential, including regular, somewhat curtailed sleep hours, excellent relaxation skills, and active waking lifestyles *(11)*. Behavioral treatments such as sleep restriction consolidation, biofeedeback, and the like, also can be helpful. Pharmacologically, benzodiazepines and zolpidem are effective as hypnotics *(9)*. Long-term use of drugs has raised the question of tolerance and dependence *(9)*. Recent studies, however, have shown that the risk for tolerance, dependence, and addiction is minimal in patients using long-term benzodiazepines for

insomnia or for other sleep disorders *(19–21)*. Another problem with the use of benzodiazepines in patients with idiopathic insomnia is the tendency among such patients to have atypical reactions to medications *(7)*; for example, little sedation from large doses of sedative/hypnotics *(7)*. According to sporadic case reports, some patients with idiopathic insomnia have responded to low-dose tricyclics, antipsychotic medications, or opiates *(7,22)*. More recently, 5 mg of melatonin has been shown to be helpful in treating chronic insomnia in school-age children *(23)*.

Case 2

A 36-year-old man presented to the sleep center clinic for a first-time evaluation concerning his long-standing inability to fall or stay asleep. He stated that as far back as he could remember, even as a child in grade school, he had trouble falling asleep. His mother told him that even as a newborn he slept much less than his siblings had. He went to bed around 10 PM and tossed and turned for an hour or so before falling asleep. He stated that his sleep was very light, and he tended to wake up once or twice in the middle of the night and stayed awake an undetermined amount of time, tossing and turning in bed. Whenever he was unable to fall asleep, he became restless, constantly watching the digital clock on his bedside table and only rarely getting out of bed to watch TV. He went to bed every night anticipating not falling asleep. As a result, he got about 4–5 hours of sleep a night, and did not feel refreshed. Sometimes, after a few bad nights during which he would hardly get any sleep, he would sleep 1 night for about 7 hours, and then would feel significantly better and refreshed in the morning. He denied excessive daytime sleepiness, and denied falling asleep in inappropriate situations. He denied being able to take naps. He stated that whether he slept at home or somewhere else, he was still unable to fall asleep and had the same trouble falling and staying asleep. He denied symptoms of restless legs or of periodic limb movements. He denied snoring, heartburn, cataplexy, sleep paralysis, hypnagogic hallucinations, or symptoms of apnea. In the past, he had tried zaleplon and trazodone. Zaleplon had not helped, and although trazodone helped him to sleep, it produced excessive daytime tiredness, grogginess, and fatigue. He also tried over-the-counter sleeping aids that did not make his sleep satisfactory in length or quality. He did not drink caffeinated beverages after the early afternoon, nor alcohol in the early afternoon, but he did chew tobacco throughout the day, even into the late evening. He had no other complaints.

His family history was significant for a similar type of insomnia in his grandmother and mother, but not in his father or siblings. Physical exam was normal. All-night PSG revealed increased sleep latency and poor sleep efficiency at 48% due to prolonged unexplained awakenings. An actigraph, worn for 1 week, confirmed his subjective reports of 4–5 hours of fragmented sleep at night.

With strict compliance of sleep hygiene regulations and 1 mg of estazolam at bedtime, he was able to improve his sleep efficiency to a considerable degree, but not resolve his insomnia entirely *(24)*.

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8

Sleep State Misperception

Stephen Duntley

DEFINITION

Sleep state misperception (SSM) is defined by the *International Classification of Sleep Disorders* (*ICSD*) as "a disorder in which a complaint of insomnia or excessive sleepiness occurs without objective evidence of sleep disturbance" *(1)*. SSM is included under the category of primary insomnias in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (2)*. It is also referred to as pseudoinsomnia, subjective complaint of disorder of initiating and maintaining sleep without objective findings, and sleep hypochondriasis.

HISTORICAL PERSPECTIVES

Awareness that objective sleep findings and subjective sleep reports may differ markedly emerged with the appearance of polysomnography as a research tool in the late 1950s. In 1959, a case study was published reporting a marked discrepancy between a patient's subjective complaint of severe insomnia and objective sleep in the laboratory *(3)*. A 1976 study of 122 patients with chronic insomnia found widespread differences between subjective and objective sleep parameters *(4)*. The discrepancy between subjective complaints of excessive sleepiness and objective findings was noted after the adoption of the Multiple Sleep Latency Test (MSLT) as an objective, validated test of daytime sleepiness *(5)*. In 1990, the term *sleep state misperception* was adopted as a diagnostic term in the *ICSD*, replacing the terms *subjective insomnia complaint without objective findings* and *subjective sleepiness without objective findings (1)*.

EPIDEMIOLOGY

The population-based incidence and prevalence of SSM is unknown. In one large series of patients presenting to a sleep disorders center, 9% of patients with insomnia and 5% of patients with excessive daytime sleepiness were classified as having SSM *(6)*. A more recent multicenter evaluation of the *ICSD* and *DSM-IV* classifica-

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tion systems found that SSM was a primary or secondary diagnosis in 6.6% of 216 patients with consecutive insomnia *(7)*.

ETIOLOGY

The etiology of SSM is not known. Some discrepancy between subjective sleep reports and polysomnographically recorded sleep is found in normal sleepers. For instance, in one study of normal sleepers, 4–8 minutes after the first sleep spindle, only 60% of individuals were aware of sleep onset, and at 16 minutes, 10% were still unaware of sleep onset *(8)*. Similarly, individuals are often unaware of being asleep when awakened from stage 4 sleep *(9)*. An attempt has been made to correlate multiple electroencephalogram (EEG) measures such as sleep stage, sleep-onset latency, waking time and arousal frequency, total sleep time, and sleep spindle density with the perception of sleep. It is clear that no single factor or combination of factors has been found to strongly relate EEG, behavioral, and subjective indexes of sleep *(10)*. Patients with insomnia tend to report more discrepancies than normal sleepers, typically overestimating sleep latency (SL) and waking time *(4,11–13)*. How this discrepancy becomes further exaggerated to a clinically significant SSM is unknown.

Salin-Pascual et al. noted that although sleep continuity measures did not differ between patients with SSM and normal controls, the sleep-stage distribution of patients with SSM was similar to that of other patients with insomnia with more stage 1 and 2 sleep and less stage 3 and 4 sleep *(14)*. Because of this finding, they suggested that SSM might represent a transitional state between normal sleep and a more extreme insomnia condition. Arguing against this view is the observation that patients with psychophysiological insomnia rarely report a history of the complete insomnia, which is so characteristic of patients with SSM. The authors also proposed that SSM may represent a distinct subclassification of primary insomnia. It has also been proposed that the hyperarousal seen in insomnia is not a unitary phenomenon but consists of three components: somatic, cognitive, and central nervous system (CNS) arousal. These three components can occur in varying degrees in different patients. According to this theory, in SSM, CNS hyperarousal is disproportionately present with relatively little of the cognitive or somatic hyperarousal, which would lead to the polysomnographic changes found in psychophysiological insomnia *(15)*.

PATHOGENESIS AND PATHOPHYSIOLOGY

The biological basis of SSM is not known. Suggested possibilities include the presence of a pre-sleep cognition that interferes with perception of sleep *(16)*, excessive mentation during sleep *(17)*, or attenuation in the mesograde amnesia that accompanies sleep *(18)*. It is also possible that a physiological abnormality exists in these patients that is not detected by standard polysomnography. For instance, it has been shown that auditory stimuli sufficient to increase arterial blood pressure or heart rate can result in daytime sleepiness despite the absence of EEG

arousals during the stimulus *(19)*. Patients with SSM have been shown to have elevated levels of physiological arousal as measured by 24-hour metabolic rate, although the increase was less than observed in psychophysioligical insomnia *(20)*. Patients with SSM have demonstrated increased activity on actigraphy during sleep *(21)*. The tendency toward mislabeling sleep as wakefulness in insomnia may reflect elevated levels of CNS arousal, and frequencies that are not normally quantified in standard polysomnography may be important markers for this elevated arousal. In one study, patients with insomnia who have low EEG α frequency activity during sleep were more likely to underestimate total sleep time and overestimate awakenings compared to patients with insomnia who have higher amounts of α frequency EEG activity *(22)*. It has also been demonstrated that increased β/γ activity is correlated with the perception of wakefulness during sleep *(23)*.

Another potential cause of SSM is the misperception or mislabeling of another bodily state such as fatigue or depression. For instance, in two recent studies, both nefazodone and fluoxetine alleviated depression and resulted in improvements in subjective sleep quality, although patients given fluoxetine showed significant declines in objective sleep characteristics such as increased number of awakenings and decreased sleep efficiency *(24,25)*. Similarly, no group difference in sleep diary measures of sleep quality was seen between patients given nefazodone or paroxetine, despite the declines in objective sleep measures in the patients given paroxetine *(26)*. Some patients may attribute daytime cognitive difficulties such as trouble concentrating or memory problems to a poor night's sleep or sleepiness, when sleep is adequate and true sleepiness is not present.

Smith and Trinder were able to simulate SSM in 20 healthy volunteers who did not have insomnia by causing microarousals from sleep through the manipulation of the sleep environment. The same individuals did not have any misperception when they were restudied on other nights when the sleep environment was not manipulated to cause the above mentioned arousals. Hence, the researchers postulated that the cause of SSM in insomniacs is due at least partly to the increased number of brief arousals from sleep *(27)*. This sleep misperception as being awake also leads to the perpetuation of the insomnia because of previous sleep being perceived as wake time *(13)*.

CLINICAL MANIFESTATIONS

Patients with SSM complain of either longstanding insomnia with difficulty initiating or maintaining sleep, nonrestorative sleep, or excessive daytime sleepiness that is not documented by polysomnography and MSLT. The patient must report that the symptoms were present during the testing. Unique to SSM is the tendency for patients to report virtually no sleep for days, weeks, or even years. They often vehemently claim that the essentially normal polysomnographic recordings are in error. Like other forms of insomnia, clinically significant complaints are accompanied by reports of waking dysfunction, such as fatigue that impairs social or occupational function and that the patient believes will improve with treatment.

Case 1

A 36-year-old female presented to the sleep center outpatient clinic for initial evaluation of a lifelong history of insomnia. She stated that as far back as she could remember, which is as young as 4 years old, she had a problem with insomnia. She stated that over the past several years her problem had worsened. There were nights when she did not sleep at all. Most nights she went to bed between 8:30 and 11 PM, and it took her 3–4 hours to actually fall asleep. She reported that she woke up after 45 minutes to 3 hours. The most she slept in a 24-hour period was 3 hours. The next day she would feel severely exhausted. She had tried and failed four different hypnotics. Despite being fatigued, she could not take naps during the day. She did not fall asleep unintentionally during the day in any situation. She denied gasping for air or symptoms of restless legs or any pains, anxieties, or worries at night. She stated that her daughter mentioned that she rarely snored. She denied any morning headaches or dry mouth. She denied cataplexy symptoms and hypnagogic hallucinations, but endorsed rare episodes (three in her entire life) of sleep paralysis. She had no allergies, was not on any medications, and had a past medical history of head banging and rocking sleep disorder as a child and a teenager. She also had a severe febrile illness as an infant. Her family history is significant for delayed sleep phase in her sister. Her social history is significant for considerable amounts of caffeine intake in the form of coffee and chocolate. A review of her systems was negative and her exam was normal.

She came in for an overnight polysomnogram (PSG). The PSG revealed 6.8 hours of sleep with 7.9 brief arousals for no apparent reason per hour of sleep. When questioned the next day as to how much she thought she had slept, she mentioned that at best 2 hours.

She was set up with an actigraph and asked to fill out concomitantly sleep logs.

Figure 1 shows her subjective perception of sleep on the sleep logs.

Figure 2 shows the objective amount of sleep she actually got as measured by the actigraph.

The results were discussed with the patient and she was reassured. She was accepting of the diagnosis. Unfortunately she was lost to followup.

DIFFERENTIAL DIAGNOSIS

The presenting symptoms of SSM may be difficult to distinguish from other forms of insomnia. SSM shares many features with psychophysiological insomnia and the underlying pathophysiology may be related. The longstanding, unremitting character of the complaint may resemble idiopathic insomnia. Inadequate sleep hygiene, generalized anxiety disorder, affective disorder, circadian rhythm disorders, and medication use and abuse may co-exist with SSM, but do not explain the

Sleep Log

Name _____ Weeks of _____

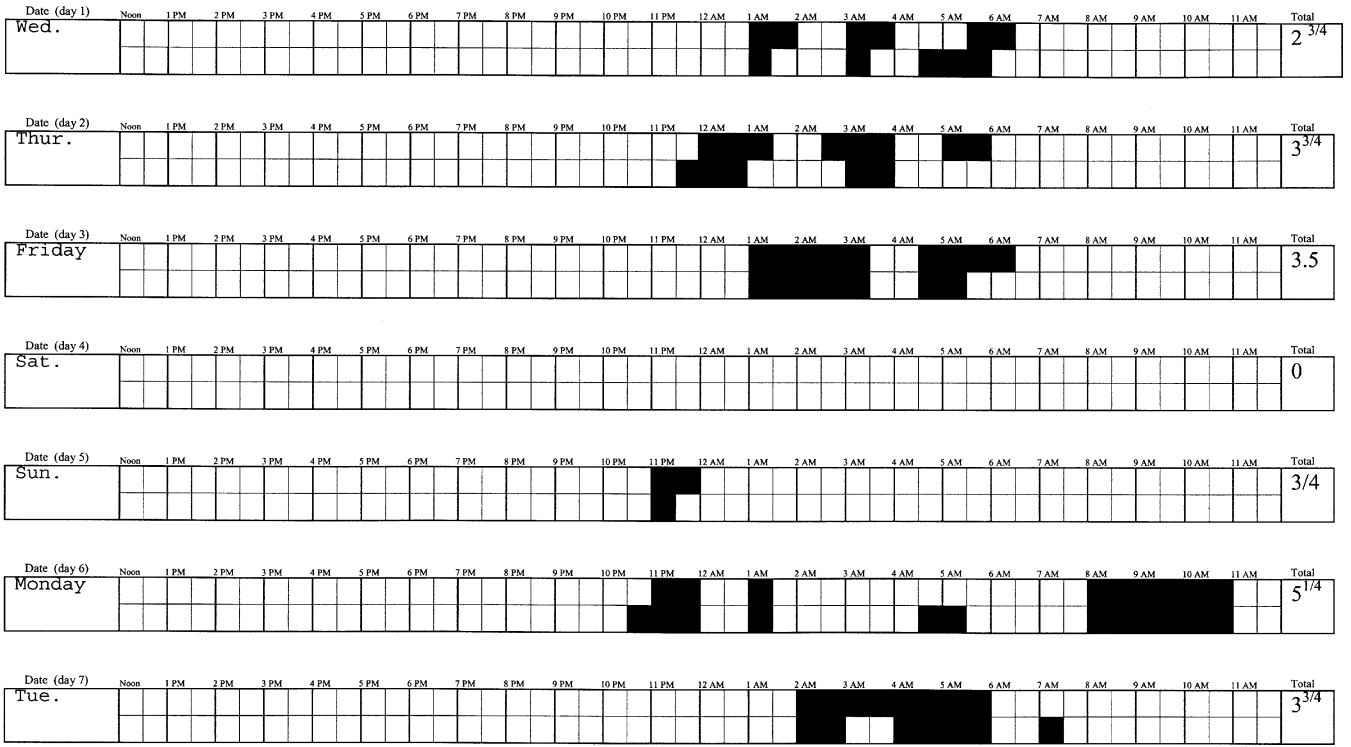

Fig. 1. Sleep log showing patient's subjective perception of sleep. Shaded areas signify sleep; open areas signify wakefulness.

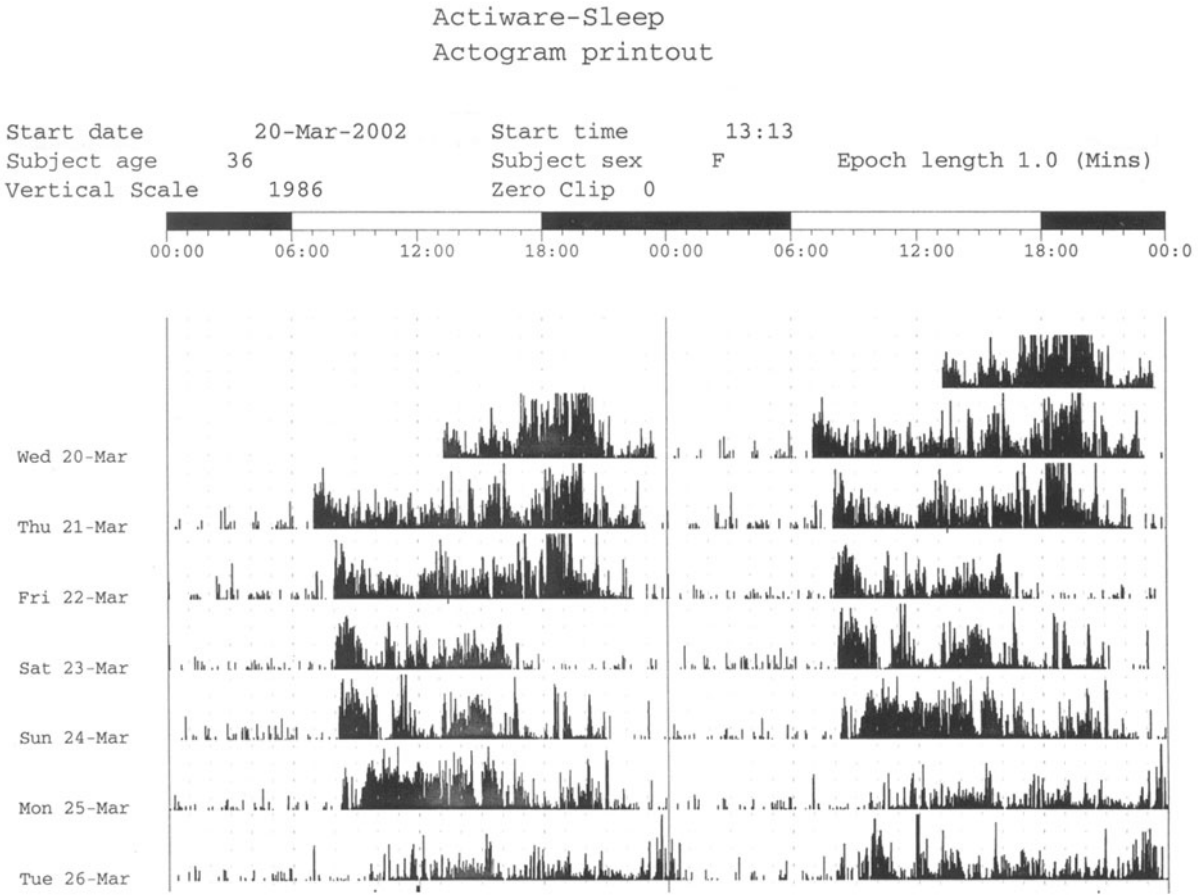

Fig. 2. The objective amount of sleep patient actually got as measured by the actigraph. High bars indicate wakefulness; low bars indicate sleep.

marked discrepancy between objectively measured sleep and subjective reports. Polysomnography is required because the distinguishing feature is normal SL and continuity measures during polysomnographically measured sleep despite the insomnia complaint. Primary sleep disorders such as sleep apnea syndrome and periodic limb movement disorder may be associated with a perception of obtaining virtually no sleep because the frequent arousals and awakenings in these disorders may not allow normal perception of sleep. Unlike SSM, sleep continuity measures in these patients are not normal, and other associated clinical symptoms usually suggest the correct diagnosis.

DIAGNOSTIC WORKUP

As with other forms of insomnia, a thorough history and physical examination are essential. The bedpartner should be interviewed if possible. Unlike other forms of insomnia, however, polysomnography is essential for the diagnosis. The *ICSD (1)* requires a PSG SL of less than 20 minutes, a minimum of 6.5 hours of sleep, and a normal number of awakenings and arousals. Additionally, MSLT should show a mean SL of greater than 10 minutes. The latter requirement is to assess for the possibility that patients with idiopathic hypersomnia may interpret daytime sleepiness as a consequence of inadequate sleep. However, because insomnia by nature varies from night to night, occasionally bad sleepers can have a good night. Therefore, the only way to diagnose SSM is if the individual states that he or she has not slept well or not at all in the lab on a given night when the PSG shows normal sleep.

Although not required for diagnosis, actigraphy may be useful in establishing the actual sleep patterns of these patients because, by definition, these indivduals are unable to give accurate accounts of actual sleep time. Actigraphy is a recently developed technique that records activity during waking and sleeping without application of any electrodes. An actigraph is worn on the wrist and is about the size of a watch. It consists of a movement detector and considerable memory, so it can record movement and nonmovement data plotted against time for 1 or 2 weeks. The patient can wear it continuously during sleep and as he or she performs routine daily activities. Actigraphy is ideal for extended examination of the sleep–wake cycle in the patient's home environment. However, there may be a discrepancy in some patients with SSM between actigraphy and polymsomnography, with wrist actigraphy registering wakefulness, while the PSG shows sleep. Increased wrist movements or similar events in these patients may be the reason they perceive themselves as awake when they are actually asleep.

PREVENTION

Because the cause of SSM is poorly understood, effective prevention is not possible. This disorder may share features with psychophysiological insomnia, thus, it is possible that measures used for the prevention of psychophysiological insomnia may also prevent SSM in some patients.

PROGNOSIS AND COMPLICATIONS

The prognosis of this group is not clearly delineated. In many patients, it is chronic and unremitting despite persistent treatment attempts. Drug dependence may develop as patients attempt to treat either perceived insomnia or daytime sleepiness with hypnotics or stimulants.

MANAGEMENT

Data on the treatment of SSM is extremely limited. Initial treatment should consist of sharing with the patient the normal results of the sleep study, and educating the patient about sleep while attempting to correct any misconceptions the patient may have. Some patients will express relief, but many will refuse to accept the results of the study. The same cognitive-behavioral techniques that are used to treat psyhophysiological insomnia may be helpful for some patients. Hypnotics may provide symptomatic improvement despite the normal sleep continuity measures, but caution should be used because of the risk of hypnotic dependence without clearly defined benefits.

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9
Sleep Hygiene

Hrayr P. Attarian

DEFINITION

The American Academy of Sleep Medicine (AASM; previously the American Sleep Disorders Association [ASDA]) classifies poor sleep hygiene-induced insomnia as one of the 13 extrinsic sleep disorders in the 1997 revised edition of the *International Classification of Sleep Disorders* (*ICSD*) *(1)*. Inadequate sleep hygiene and extrinsic sleep disorders are those sleep disorders caused or maintained by forces outside the body, as opposed to intrinsic sleep disorders (e.g., narcolepsy, obstructive sleep apnea syndrome or psychophysiologic insomnia), which are conditions where the pathophysiology depends on factors within the body. In extrinsic sleep disorders, external factors are primarily responsible for producing the symptoms. Removal of these factors is the first step of treatment and almost always ameliorates if not completely resolves the disorder. Although the distinction between intrinsic and extrinsic sleep disorders is clear, the two may co-exist and/or interact in an individual patient. Volitional extrinsic factors may initiate the processes responsible for the development of some intrinsic sleep disorders, becoming internalized as the disorder develops. For example, psychophysiological insomnia can develop after years of extrinsic sleep-destroying habits collectively known as inadequate or poor sleep hygiene. Sleep hygiene refers to one's engaging in a set of behaviors that are conducive to falling asleep and staying sleep and abstaining from behaviors that are not. For example, intake of caffeinated beverages very close to bedtime produces insomnia resulting from caffeine's stimulating properties, thus constituting poor sleep hygiene. Setting aside relaxation or "down time" prior to going to bed facilitates sleep, therefore making it an element of good sleep hygiene.

The *ICSD* defines inadequate sleep hygiene as a sleep disorder resulting from the performance of daily living activities that are inconsistent with the maintenance of good-quality sleep and full daytime alertness *(1)*.

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EPIDEMIOLOGY

There are no ethnic or racial predilections identified in poor sleep hygiene insomnia and men and women are affected by it almost equally. Older teenagers and young adults are one of the two groups especially affected by poor sleep hygiene. Manni et al. studied a large group of 17-year-old Italian high school students. In this cohort, 19% of girls and 11.6% of boys had persistent insomnia due to poor sleep hygiene *(2)*. The other group especially affected is comprised of the elderly, especially those dwelling in nursing homes *(3)*. This is probably resulting from the level of noise and ambient light present in this situation *(4)*.

Patients suffering from chronic insomnia exhibit a complex interplay of internal factors and poor sleep hygiene behaviors. It is impossible to tease out the magnitude of the roles each element plays in the development of the insomnia. Most patients suffering from chronic and persistent insomnia have at least some features of inadequate sleep hygiene admixed with the features of their primary disorder. It is not known whether the sleep hygiene components are a result, or a partial cause, of the main sleep problem. There is, however, evidence to suggest that sleep hygiene education is at least partially effective in patients with primary insomnia *(5,6)*. In a survey conducted among 3600 adult Japanese women to identify external factors causing insomnia, the prevalence of insomnia was found to be 11.2% *(7)*. Most complaints of insomnia were related to nighttime street noises.

ETIOLOGY

As discussed previously, the main cause of poor sleep hygiene insomnia is the set of behaviors in which patients voluntary engage. These behaviors produce increased arousal or in some way disrupt normal sleep *(1)*. These behaviors are normal when practiced in moderation but cause insomnia when they occur in susceptible people or in conjunction with other factors that disrupt sleep. Common poor sleep hygiene practices include going to bed when not feeling sleepy; consuming moderate amounts of alcohol, caffeine, or nicotine close to bedtime; night-to-night variability in bed and wake times; excessive napping, especially when done in close proximity to the major sleep period; stimulation near bedtime (psychosocial stress, excitement, physical exercise, stimulating mental activity, etc.) *(8)*; poorly regulated environmental elements such as ambient noise *(7)*, light, or temperature *(8)*; or disturbing household members *(9)*. A study done in community-dwelling Japanese women found that living close to streets with high nighttime traffic was the most important external risk factor for developing poor sleep hygiene insomnia. Others included experiencing major life events, having children under the age of 6 years, and having an irregular bedtime *(7)*.

PATHOGENESIS AND PATHOPHYSIOLOGY

Not every individual who practices poor sleep hygiene develops insomnia. Persons diagnosed with inadequate sleep hygiene insomnia have an underlying hyper-

Table 1
Sleep Hygiene Guidelines Used at Washington University Sleep Medicine Center

1. Go to bed only when sleepy.
2. Use the bed only for sleeping. Do not read, watch television, or eat in bed.
3. If unable to sleep, get up and move to another room. Stay up until you are definitely sleepy and then return to bed.
4. Set the alarm and get up at the same time every morning, regardless of how much you have slept through the night.
5. Do not nap.
6. Do not exercise just before going to bed.
7. Do not engage in stimulating activity just before bed.
8. Avoid caffeine in the afternoon.
9. Do not drink alcohol close to bedtime.
10. Eliminate clocks in the bedroom.
11. Before bedtime, schedule a period to review stressful events of the day.
12. Promote relaxation and sleep by focusing on quiescent tasks that occupy the mind such as reading, watching television, or listening to music.

Table 2
Amount of Caffeine in Common Beverages

Beverage	Amount of caffeine
1 cup of brewed coffee	100–150 mg
1 cup of instant coffee	85–100 mg
1 cup of tea	65–75 mg
12 ounces of cola	40–75 mg
1 cup of cocoa	50 mg

sensitivity to changes in their sleep schedules and minute amounts of external stimuli. They have exaggerated physiological responses to even small amounts of stimulants (caffeine, nicotine), alcohol, exercise, excitement, or strong environmental disruptions, such as noise, shift work, and ambient light. It is thought that these persons' circadian control centers (suprachiasmatic nucleus) *(10)* also seem to be sensitive to even minimal variations in their sleep schedules or to daytime napping *(1)*. Others who suffer from inadequate sleep hygiene insomnia because of psychological or physical illness or because of an innate predisposition, may have a particularly low tolerance to the effects of even infrequent sleep deprivation and, in good faith, in an attempt to remedy the situation may resort to such poor sleep hygiene behaviors as extra naps or bedtime alcohol. A combination of behaviors that are nonconducive sleep and an innate physiological hyperarousal leads to the development of poor sleep hygiene insomnia *(11,12)*.

CLINICAL MANIFESTATIONS

The main clinical symptom of inadequate sleep hygiene is insomnia. Other symptoms may include dysphoric mood, fatigue, irritability, occasional hypersomnia, and poor concentration. The time course of poor sleep hygiene-induced sleep problems may vary from self-limiting and transient, to occasional or even frequent but intermittent, or persistent. It may be the cause of insomnia or may exacerbate an already existing one or itself may be the result of a pre-existing primary or secondary insomnia. The insomnia may be sleep-onset, sleep maintenance, or terminal resulting in early morning awakenings. In some cases, it may present as irregular sleep patterns. The activities that constitute poor sleep hygiene and lead to poor sleep hygiene insomnia usually are common activities of daily life, which produce sleep disturbances in people with an innate susceptibility. Behaviors that are considered nonconducive to sleep include caffeine intake late in the afternoon or evening, alcohol intake at night (often in an attempt to self-medicate), psychological stress or excitement in the evening, obsessive clock watching while awake at night, exercise or smoking late at night or close to bedtime, use of the bed for activities unrelated to sleep (other than sex), variable bedtime and rise time, going to bed when not sleepy, poorly regulated comfort measures in the bedroom such as temperature, light, noise, uncomfortable bed, pets, and family members or housemates who may engage in behaviors that are disruptive to one's sleep *(13)*. Usually, in addition to an innate susceptibility, a combination of these behaviors and extrinsic factors is needed, any one of which might be considered acceptable behavior in most people.

Case 1

A 46-year-old engineer presented with the complaint of sleep maintenance insomnia. The patient had a bedtime between 10 and 11 PM, and had no difficulty initiating sleep. He reporting awakening everyday at around 3 AM. He subsequently was unable to return to sleep for the rest of the morning. This problem was of about 2–3 years in duration. Over-the-counter hypnotics did not help. The patient denied pain, worry, or anxiety at night. He had no history of snoring or witnessed apneas, falling asleep unintentionally during the day, or any caffeine intake after an early morning cup of coffee. He denied any neurovegetative symptoms of anxiety and depression. He was taking Zestril and Lipitor. The patient's exam was normal and his Beck's Depression Inventory score was 4 (not depressed). When further questioned, he revealed that he drinks on a nightly basis and over the past several years has three glasses of wine or some other type of liquor just before going to bed. He does this out of habit and denied having had problems falling asleep prior to engaging in this nightly alcohol consumption. He was asked to reduce his alcohol intake and to drink lesser amounts earlier in the evening.

At the next visit, 6 weeks later, his insomnia was resolved.

Case 2

A 26-year-old psychology student presented to the sleep medicine center's clinic for initial evaluation of recent sleep-onset initiation insomnia. In the past, she had only rare problems falling and staying asleep. About 6–7 months prior to coming to the center, the problem became persistent.

Currently, she goes to bed exhausted, sleepy, around midnight or 1 AM but is still unable to fall asleep. She lays in bed anywhere from 30 minutes to 3–4 hours tossing and turning, but does not leave the bed or the bedroom. She usually gets up at 7 AM with an alarm and on weekends, when she doesn't have to go to work, she sleeps into late morning and sometimes, until early afternoon.

During the day, she takes a 45- to 90-minute nap. She also uses her bedroom during the day to study, eat, watch television, read, and sometimes works late into the night shortly before retiring. She does not abuse caffeine and uses alcohol only socially. She does not abuse recreational drugs and does not smoke. She denies cataplexy, hypnagogic hallucinations, snoring, choking spells, falling asleep unintentionally during the day, or symptoms of restless legs. The only symptom she states that she has experienced is rare periods of sleep paralysis, maybe two to three times in her life time. She has a past medical history of attention deficit hyperactivity disorder. She is taking Dexedrine and Ambien when needed. Her exam is normal and her Beck's Depression Inventory score is 6 (not depressed).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of poor sleep hygiene insomnia includes three main categories of disorders. The other extrinsic sleep disorders are environmental sleep disorder; adjustment sleep disorder; sleep-onset association disorder; nocturnal eating or drinking syndrome; limit-setting sleep disorder; food allergy insomnia; insufficient sleep syndrome; altitude insomnia; the hypnotic-, stimulant-, and alcohol-dependent insomnias; and toxin-induced sleep disorder *(1)*. Sometimes, it is hard to differentiate individual disorders from each other because of significant overlap among them.

The second main category is the primary insomnias, which include psychophysiological insomnia, childhood-onset, or idiopathic insomnia, and sleep state misperception insomnia *(1)*. Any of these may co-exist with poor sleep hygiene and may cause or be exacerbated by it.

The third category is the secondary insomnias, including insomnia due to other sleep disorders such as obstructive sleep apnea, restless legs syndrome, periodic limb movement syndrome, and even narcolepsy. Insomnia can be caused by a variety of neurological, psychiatric, and other medical illnesses. Degenerative neurological illnesses, anxiety disorders, asthma, and so on, are some examples. When the symptoms of the underlying disorder are prominent, secondary insomnias are usually suspected and diagnostic testing appropriate to the circumstance may elucidate the underlying cause of the insomnia.

DIAGNOSTIC WORKUP

The diagnosis of inadequate sleep hygiene is best made through careful and detailed history of the patient's daily sleep-related habits *(13)*. These include bedtime, rise time, time spent in bed awake, different nonsleep-related activities in which the patient engages in the bed and the bedroom including watching TV, reading, and so on, timing of exercise, activities engaged in prior to bedtime and while awake at night, amount and timing of caffeine or alcohol ingestion, and daytime napping. In short, the diagnosis should try to identify any activity that is not compatible with sleep.

A useful diagnostic tool is a detailed sleep questionnaire completed by the patient and the bedpartner *(14,15)*. As in most primary insomnias, sleep diaries are essential tools in identifying sleep problems and charting their evolution and response to treatment. In a paper published in 1998, Blake and Gomez introduced a simple but useful questionnaire by which to measure compliance with sleep hygiene education *(16)*. As in most insomnias, a thorough psychiatric and medical evaluation, including a physical exam, should be done to rule out medical or psychiatric causes of the insomnia.

Per ASDA (now AASM) guidelines, polysomnography is not indicated in routine evaluation of insomnia, except when the diagnosis is uncertain and a primary sleep disorder is suspected, and when insomnia does not respond to appropriate behavioral and pharmacological treatments *(17)*.

PROGNOSIS AND COMPLICATIONS

As in most extrinsic sleep disorders, once the underlying cause is removed, the symptoms resolve completely. The sooner treatment is started, the more complete the resolution of symptoms, and the better the prognosis. If poor sleep hygiene is allowed to continue, psychophysiological insomnia may result in susceptible individuals. Some recent publications find a high correlation between poor sleep hygiene, especially among younger drivers and high accident rates *(18,19)*.

PREVENTION

Education is the cornerstone for the prevention of poor sleep hygiene insomnia. Almost everyone engages in poor sleep hygiene at various times. There is also a large number of external sleep disruptors such as noise, ambient light, and so on, outside of one's control. Although it is extremely important to educate people about sleep hygiene, these rules do not strictly apply to everyone. A short daily nap is part of the lifestyles of some cultures and does not necessarily constitute poor sleep hygiene if it does not result in symptoms of insomnia or sleep disturbances. Similarly, a cup of coffee or a drink with dinner or even reading in bed may not negatively impact some people's sleep. However, either because of their predisposition or because of the additive effect of different factors, some people may develop significant insomnia.

It is essential to inform people, at the first appearance of symptoms of the potential sleep problems that poor sleep hygiene can cause, and help identify and stop them.

TREATMENT

Like all extrinsic sleep disorders, the mainstay of treatment needs to be modification or complete removal of the external factors causing the insomnia. Sleep hygiene must be taught and reinforced in patients suffering with this disorder *(20)*. It may be overwhelming for patients to follow every single sleep hygiene regulation at once. This may lead to noncompliance. It is best to isolate two or three key factors individualized to the patient and ask the patient to concentrate on those *(13)*. Other cognitive-behavioral treatment modalities may be helpful in select cases. These include relaxation therapy, biofeedback, sleep-restriction consolidation, and stimulus control therapy *(13)*. Usually, however, sleep hygiene education is simpler, easier to follow, and as effective as the more elaborate and difficult to follow cognitive-behavioral therapy. In fact, of all the nonpharmacological/behavioral treatments, sleep hygiene education is one of the most effective methods and one of the easiest to follow *(6)*.

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III The Secondary Insomnias

10

Insomnia Caused by Medical and Neurological Disorders

Kenneth E. Plotkin

Any systemic or neurological condition can cause sleep disruption. Diseases of the central nervous system (CNS) in particular may profoundly affect sleep initiation and maintenance by disrupting the structural and neurochemical substrates that regulate sleep. Medical conditions can lead to chronic insomnia in several ways. They may cause unpleasant stimuli, which in turn disrupt sleep continuity. They may produce changes in systemic physiology that are vital to sleep continuity (as with disorders of ventilation), or they may produce humoral changes that favor awakening (as in thyroid or adrenal disease). The incidence of insomnia increases with age as medical problems increasingly occur *(1)*, and patients with chronic insomnia are more likely to develop adverse health outcomes due to medical disease *(2)*. The effects of acute and subacute sleep disruption can lead to psychophysiological insomnia by creating the anticipation of disturbed sleep and altering circadian rhythms, further accentuating the disruptive effects of the underlying medical condition. Difficulties with insomnia may persist long after the causative medical condition has been effectively managed.

When describing the medical causes of insomnia, the most frequently recurring theme is the disruptive influence of painful or unpleasant stimuli on sleep initiation and maintenance. The polysomnographic appearance of sleep disturbance caused by medical conditions is nonspecific, and most times is no different than any other form of insomnia. The diagnosis is mostly made by clinical correlation, requiring a thorough review of a patient's general medical profile and a complete physical examination. After a polysomnogram (PSG) has been recorded to evaluate for any clear physiological causes of sleep disruption, an empirical approach to treatment can begin.

Treatment of secondary insomnia draws on all of the commonly utilized behavioral, pharmacological, and alternative medical approaches utilized in primary insomnia. Optimizing the treatment of the underlying medical condition is the cornerstone of effective insomnia management, along with attempts to improve the

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quality of sleep. Ultimately, the treatment must also take into consideration potential complications produced by the medical condition(s), either a change in the natural course of the disease, or an untoward response to well-intended pharmacological insomnia therapy. In cases where the medical condition has an intermittent character, shorter term or intermittent insomnia treatment may be the best approach. In progressive medical disorders, the management of associated insomnia may require elaboration over time. More complicated cases should compel frequent review of the applied management strategies, in order to avoid the maintenance of suboptimal therapy, the continuation of pernicious medications, and the ultimate surrender of the patient to decline in level of function as sleep disruption becomes more profound.

An attempt to comprehensively review major medical disorders is bound to leave some conditions unaddressed. For most conditions there is, at best, anecdotal information regarding insomnia as a feature of the disease process. Perhaps the best way to frame the discussion is an approach to each organ system, allowing for the collection of related disorders that may share a common overall effect on sleep continuity. This parallels the method used by physicians to categorize the symptomatic profile (the Review of Systems) for a given patient, allowing for an orderly review of potential medical issues during a general medical examination. The unique role of each organ system in sleep disruption can be reviewed, even for disorders of completely disparate etiology (e.g., a neoplastic vs inflammatory cause of disease), along with the shared treatment issues.

The skin is the body's largest organ, serving to sequester and protect the internal environment from the outside world, and providing some of the most profound early alerts of important environmental issues. It has the densest collection of nerve terminals outside of the CNS. Any condition that imposes damage, pressure, or irritation on the dermis will cause pain through dermal nerve endings, and the pain will disturb the integrity of sleep. Infectious, allergic, or inflammatory skin conditions are common potential causes of disturbed sleep initiation and maintenance. Pain due to minor or major burns frequently delay sleep initiation, and may become aggravated by involuntary body shifting during sleep. The acute phase of burn healing may be incredibly painful and may last several months in severe cases, and this is the time of greatest sleep disturbance. The healing process may leave scar tissue that is unusually sensitive or restrictive, prolonging the negative influence on sleep quality. In a cohort suffering from herpes zoster reactivation, insomnia was one of the most bothersome symptoms reported (25%), second only to pain *(3)*. Lacerations have a shorter healing time, but may produce nerve injury, and the subsequent re-innervation can cause paroxysms of sharp, burning, or dull aching pain. Swelling of soft tissues due to edema may be transient, intermittent, or chronic, but causes epidermal discomfort that delays sleep onset and impairs sleep maintenance. Pathological diaphoresis may be sufficiently severe to cause awakening due to cold, damp bedclothes or sheets *(4)*. The use of occlusive dressings, bandages, or splints may produce discomfort and restrict movement during sleep. Oral corticosteroid medi-

cations may produce insomnia *(5)*, particularly at higher doses, especially during the initial period of use.

Amelioration of a skin condition may require a relatively short duration of treatment, and therefore may cause only short-term sleep disruption. The use of hypnotic medication, especially shorter acting medications that are unlikely to produce daytime sedation, may be ideally suited to a skin condition that has brief course (such as poison ivy dermatitis) or intermittent exacerbation (such as eczema). Many of the antihistamine medications used to reduce allergic response and itching are sedating, improving sleep initiation and maintenance somewhat, but may cause residual daytime effects on alertness and cognitive performance *(6)*. The use of medications such as amitriptyline or trazadone, which may improve the component of insomnia caused by depression and pain, should be considered if duration and severity of insomnia warrants their use, and if other medical conditions do not preclude their use.

Problems in the nasopharynx, oropharynx, and larynx are a common cause of sleep disruption. The most widely recognized condition that can be caused by the pharyngeal tree is obstructive sleep apnea (OSA), which can be seen in association with conditions such as nasal polyps, excessive submucosal oropharyngeal adipose tissue, oropharyngeal or nasopharyngeal mass lesions, macroglossia, uvular hypertrophy, retrognathia, and pharyngeal muscle weakness. The neck may permit OSA to occur if it is short, broad, restricted in motion, or has anterior adipose deposition. Mass lesions, hyoid pathology, and cervical spine degenerative changes can also cause OSA. Sleep apnea can produce secondary insomnia through chronic disruption of sleep continuity, and secondary insomnia in turn makes patients less tolerant of treatment with continuous positive airway pressure (CPAP) ventilation. The diagnostic PSG will show worsened sleep efficiency, less deep sleep, more frequent arousal from sleep, and longer arousal when OSA is complicated by insomnia. Upper airway resistance syndrome (UARS) may typify such a condition, where less severely disordered breathing causes a disproportionately profound degree of sleep disruption.

When insomnia complicates UARS and OSA, treatment with CPAP is poorly tolerated and may require the adjunctive use of sedating medications, which will worsen obstructive breathing to some extent. The availability of auto-titrating CPAP and biphasic ventilation units may allow for more comfortable treatment, adjusting the level of positive pressure required to overcome airway obstruction at any given time. However, even the automatic changes in pressure settings may cause arousal in a patient who suffers from insomnia. Because CPAP therapy is the most universally effective method of treating obstructive breathing during sleep, the addition of a medication to improve sleep initiation and continuity is a reasonable option. Shorter acting hypnotic medications (estazolam, zaleplon, zolpidem) will least affect the overall architecture of sleep, but will only provide benefit for the initial hours of sleep. Re-dosing of these medications may be considered, with the caveat that patients are more likely to awaken with a "hangover" effect that mitigates some

of the therapeutic efficacy of CPAP. Longer acting hypnotic medications (temazepam, clonazepam, diazepam, lorazepam) produce more alteration in sleep architecture, and are more likely to have residual morning sedation as a side effect, in addition to having more profound muscle relaxant effects that may worsen the magnitude of obstructive breathing. Tricyclic antidepressant medications (such as amitriptyline, nortriptyline, and trimipramine), trazadone, or a sedating antihistamine may help improve sleep initiation and continuity, but their side effects may include daytime sleepiness and mucosal dryness, which aggravates the drying effect of CPAP therapy on nasopharyngeal and oropharyngeal mucosa.

Postnasal drip caused by chronic allergic rhinitis or chronic/recurrent sinusitis may cause frequent awakening by stimulating cough during sleep. Allergic, infectious, or inflammatory pharyngitis can impair sleep continuity through the occurrence of local pain, which may be worsened on swallowing, or may stimulate frequent reflexive swallowing. Sleep-related laryngospasm *(7)* or choking *(8)* has been described, and may cause sufficient distress that the security of sleep is threatened. Any painful condition affecting the airway can negatively affect the quality of sleep, and when present for a sufficient duration or with sufficient frequency, can cause secondary insomnia. Assessment of the head and neck may not provide sufficient evidence of pathology in some cases. The diagnostic clue on a routine PSG would be frequent bursts of submental myogenic activity, which in isolation could also be interpreted as bruxism or a reflection of a nocturnal periodic movement disorder. In this case, the bedpartner's observations or the use of good quality video/audio during PSG may help to identify the cause of sleep disruption, and help to appropriately direct treatment.

Pulmonary disorders frequently cause some degree of sleep disruption, which can develop over time into secondary insomnia. Asthma *(9–11)*; chronic obstructive pulmonary disease *(12,13)*; restrictive changes in the pulmonary bed *(14)*; bronchitis, pneumonitis, pleuritis, and neoplasia of the pulmonary tree can cause disruption of ventilation, waxing/waning hypoxia *(15)*, chest wall pain, and cough that lead to frequent arousal and poor sleep continuity. Chronic hypoxia and hypercarbia gradually desensitize carotid and CNS medullary chemoreceptors, causing central apnea that can worsen the magnitude of ventilatory pathology, and thereby the chronic nature of sleep disruption. Medications used to treat asthma, including bronchodilators such as albuterol, the methylxanthines derivatives theophylline and caffeine, and even inhaled steroid medications have an activating effect on the CNS, prolonging sleep initiation and increasing the likelihood of arousal from sleep. The appearance of sleep-disordered breathing in association with pulmonary disease is well appreciated by the medical community, but optimal sleep quality may not immediately return despite appropriate management of the pulmonary problem. Medications used in the treatment of secondary insomnia due to pulmonary dysfunction must be chosen carefully. The level of oxygenation and the persistence of ventilatory drive may be challenged by even the short-acting hypnotic medications, and hypnotics with more muscle-relaxing qualities may com-

promise the additional ventilatory effort offered by chest wall musculature. The use of tricyclic antidepressant medications is relatively contraindicated in asthma, due to their propensity to aggravate bronchiolar constriction. Nonpharmacological treatments (sleep restriction, light therapy) may be paired with very low doses of short-acting hypnotic medications to enhance sleep initiation and continuity, and the serotonin reuptake inhibitor paroxitine may have slightly sedating and anxiolytic properties that prove useful for the treatment of secondary insomnia due to pulmonary disease.

Cardiovascular diseases cause sleep disruption through nocturnal angina *(16,17)*, abnormal sensations such as palpitations or tachycardia *(18)*, paroxysmal dyspnea, or orthopnea related to congestive heart failure (CHF). More severe CHF produces ventilatory changes during sleep as well, with periodic breathing of Cheyne-Stokes character, or central apnea that produces frequent arousal. Orthopnea may require that a patient recline only slightly from a sitting position, and the disturbance of sleep continuity may be dramatic. Acute insomnia is a common sequela of myocardial infarction *(19)*. The medications used to treat cardiac disturbance may aggravate sleep disruption. Vasodilating agents may produce headache that disrupts sleep continuity, as may the rebound effects of morphine when it is used intermittently. Digoxin may produce side effects including insomnia and headache, especially at higher blood levels. Diuretic therapy at night causes frequent awakening to urinate. The symptoms of cardiac disease and potentially pernicious effects of its treatment are usually superimposed on the typical sleep fragmentation of elderly individuals, but the chronicity and severity of cardiac disturbance will largely determine whether secondary insomnia becomes sufficiently severe to require treatment. Once medical therapy has been optimized, the ideal approach will select therapy that has the least chance of casing medical complications. As with severe pulmonary disease, longer acting hypnotic medications are more likely to cause ventilatory compromise. Tricyclic antidepressant medications can increase the possibility of cardiac arrhythmia, and are relatively contraindicated. Trazadone may be somewhat less likely to cause arrhythmia, but like the tricyclic agents, its residual effects in the daytime may cause fatigue or hypersomnia. Creative treatment with shorter acting hypnotic medications may be combined with efforts to maximize physical comfort through special furniture, such as a hospital bed, to promote blocks of restful sleep lasting a few hours at a time. Monophasic sleep may need to be sacrificed, in favor of two or three smaller blocks of sleep that take advantage of the natural periods of drowsiness that occur during the day. Treatment of disturbed ventilation may help sleep continuity, avoid hypoxia, and provide more refreshing sleep, but CPAP therapy is not well tolerated, and can actually aggravate central apnea. Biphasic positive pressure ventilation may avoid exacerbation of central apnea, and may be more tolerable in its promotion of normal ventilatory tidal movement.

Disorders of the gastrointestinal (GI) system may produce significant sleep disturbance leading to secondary insomnia. The primary problem may remain occult, even as PSG and attempts at therapeutic management proceed over the course of

months or years. The effects of gastroesophageal reflux disorder (GERD) *(20)* and peptic ulcer disease *(21)* on sleep have led to their inclusion in the *International Classification of Sleep Disorders* diagnositic and coding manual. GERD worsens with reclining, especially if a person has eaten within 1 or 2 hours of sleep. GERD is also worsened by obstructive breathing, as increased in intrathoracic pressure produces an increase in abdominal displacement, causing more pressure within the GI lumen and more tendancy for reflux through a hypotonic or incontinent lower esophageal sphincter. The irritation of the esophageal mucosa causes arousal from sleep, which appears on PSG to be spontaneous, without correlation on ventilatory or electromyogram channels. Only the use of a nasogastric pH probe during PSG will provide definitive diagnosis, but most sleep laboratories do not routinely perform such testing. Peptic ulcer disease is likely to be identified due to its typical pattern of awakening in the early hours of sleep, with abdominal discomfort or nausea. The untreated condition could certainly produce chronic sleep disruption, but recurrent bouts of ulcer may eventually lead to chronic difficulties with sleep maintenance and persistent early awakening. Pain and discomfort in association with any infectious, inflammatory, allergic, or neoplastic intestinal disorders may cause frequent nocturnal arousal, which may also include prolonged awakenings for bathroom visits, requiring sleep to be reinitiated at a disadvantageous time during the night. Milk *(22)* and other food allergies *(23)* have been suggested as a cause of poor sleep in infants. The absence of a specific finding on PSG makes it contingent on the clinician to infer the diagnosis from clinical history, and treatment of the underlying disorder can be combined with short-term or longer term treatment of secondary insomnia, which is likely to require at least some pharmacotherapy. The symptoms of esophageal reflux may be reduced by smoking cessation, weight loss, avoiding fatty/spicy foods, reducing daily caffeine intake, and treatment with a variety of medications, including antacids, H2-receptor blockers, proton pump inhibitors, and agents that improve gastric motility. Flexible dosing of shorter acting hypnotic medications may be most appropriate for disorders that have waxing and waning symptoms (inflammatory bowel disease) that appear at different times of night. Longer acting hypnotic medications may be required when symptoms are more severe or enduring on a given night. Note that nearly all of the hypnotic medications can aggravate intestinal problems by dehydrating mucosal linings (tricyclic antidepressants, antihistamines), increasing motility (serotonin reuptake inhibitors), or decreasing motility (benzodiazepines, barbiturates).

Urological disorders cause sleep disruption by compelling frequent awakening for urination and frequent arousal due to pain. Progressive prostatic hypertrophy compels frequent voiding of small urine volumes, ameliorated somewhat by medications that reduce the size of the prostate. Prostatic carcinoma may cause a similar pattern, and resection of the prostate may produce urinary urgency and incontinence, further exacerbating sleep dysfunction. Pain or discomfort related to interstitial cystitis, prostatitis, bladder infection, or nephrolithiasis may cause awakening or occult nocturnal arousal, resulting in insufficient sleep. Neurogenic bladder dys-

function may produce a hypotonic (overfilled) bladder that requires intermittent catheterization to avoid overflow incontinence, or a hypertonic bladder that produces discomfort and the urge to void with the smallest amount of urine volume. Once the cause of urological dysfunction has been identified and appropriately addressed, the use of hypnotic medications tend to be benign, and the pharmacology of different medications can be chosen for the most practical solution. Tricyclic antidepressant medications tend to cause urinary retention and increase urinary hesitancy, and would not be an ideal choice. Chronic renal disease commonly causes insomnia *(24)*, worsened by electrolyte fluctuations caused by hemodialysis and the high incidence of periodic limb movement disorder (PLMD).

The rheumatoid disorders, and musculoskeletal discomfort in general, are highly associated with chronic sleep disruption. Rheumatoid arthritis *(25,26)*, ankylosing spondylitis *(27)*, systemic lupus erythematosis *(28)*, vasculitis, polymyalgia rheumatica, and fibromyalgia *(29)* can produce sleep disruption, which may become a very debilitating aspect of the disease, complicating functional recovery. Daytime pain is reported to be worse following unrefreshing sleep *(30)*. The pain certainly is a profound trigger of sleep disturbance, as are the effects of glucocorticoid medications *(31)* commonly used to treat the rheumatoid diseases. The electroencephalogram (EEG) during non-rapid eye movement (NREM) sleep may include considerable alpha range activity, even in deep sleep (the "alpha-delta" sleep pattern), but alpha intrusion is not specific to the rheumatoid disorders. The same pattern may be seen in chronic fatigue syndrome *(32)*, with its cardinal symptoms of idiopathic fatigue, headache, arthralgia, myalgia, and insomnia *(33)*. Osteoarthritis may become more symptomatic as the morning approaches, after a night of relative immobility, and may result in early awakening. Degenerative change of the spine, scoliosis, and scleroderma may cause impaired ventilation, which causes frequent arousals and impaired sleep.

Various endocrine disturbances cause insomnia, because of either the activating effects of the hormones or the somatic discomfort produced by their imbalances. Insomnia is more prevalent in hyperthyroidism, in association with a globally activated behavioral state, and sleep studies have shown an overall increase in the percentage of deep sleep *(34)* once difficulties with sleep initiation are overcome. The return to a serological and clinical euthyroid state may not guarantee the resolution of insomnia. Hypothyroidism more commonly causes fatigue and lethargy, and PSG has shown an associated decrease in deep sleep. Adrenal dysfunction causing catacholamine secretion will cause sympathetic activation and insomnia, and excessive glucocorticoid levels also cause insomnia *(5,31)*. It has been suggested that elevated glucocorticoid levels may alter the production of endogenous γ-aminobutyric acid (GABA)-related steroid production *(35)*, causing some of the observed insomnia. Disruption of the hypothalamic–pituitary–adrenal axis has been found in association with chronic insomnia, although it is not clear whether the disruption of hormonal secretion is cause or effect of insomnia *(36,37)*. There is considerable clinical reporting of insomnia during menses *(38)*, with or without

associated somatic discomfort, and during menopause *(39)*. Insomnia is reported in up to one-third of patients with diabetes mellitus *(40)*. Treatment of sleep disruption in endocrine disturbance may be complicated by hormonal fluctuations and potential medical complications of therapy, and may require multiple modalities, spanning the pharmacological, behavioral, and alternative therapeutic realms.

Pregnancy may induce changes in sleep, which are observed to be most profound in the first and third trimesters *(41)*. The insomnia seen in the first trimester of pregnancy may be related to hormone fluctuations, whereas the insomnia associated with the third trimester is typically caused by physical discomfort including a firm, enlarged abdomen, urinary frequency, backache, hip ache, and fetal movements *(42)*. One study found that insomnia was reported more frequently in multiparous (vs nulliparous) women *(43)*. Changes in sleep architecture have been shown to include increased waking after sleep onset (WASO) and lower sleep efficiency, along with decreased percentage of REM sleep *(44)*. Sleep problems during pregnancy are frequently followed by postpartum sleep disruption caused by a polyphasic sleeper (the neonate), and the incidence of maternal insomnia and depression has been shown to increase when an infant has significant sleep problems *(45)*. Treatment of insomnia during pregnancy and breastfeeding provides a therapeutic challenge. Concerns must include the health of the developing child, to whom some amount of medication is inevitably transferred, potentially affecting the developing CNS *(46)*. In most cases of pregnancy and lactation, it is best to apply conservative behavioral and environmental treatment measures *(47)*. In severe cases of insomnia, pharmacological options can be used with the recognition that most have an unknown effect on human fetal development, and some actually are contraindicated. In one study *(48)*, benzodiazepines were shown to account for the greatest number of psychotropic medication exposures during pregnancy. They were mostly utilized to treat anxiety and insomnia, and no clustering of fetal malformation was observed in the population studied.

Cancer may produce insomnia due to pernicious effects on systemic physiology, painful tissue changes, therapeutic efforts, or the anxiety and depression accompanying the diagnosis. Insomnia has been found to occur in more than half (53%) of the patients with newly diagnosed lung cancer, and was felt to be a severe symptom in more than one-quarter *(49)*. Insomnia occurred in 19% of women with breast cancer, and was of chronic character 95% of the time *(50)*. Insomnia has been examined in a variety of cancer types *(51)*, and has been found to occur in about one-third of cases, along with reports of fatigue, leg restlessness, and excessive sleepiness. The fatigue associated with cancer treatment may in part be due to insomnia *(52)*. The claudication associated with hematologic disorders such as sickle cell anemia causes severe intermittent sleep disruption *(53)*, made worse by occult sleep-disordered breathing and PLMD. Treatment should take into consideration the anticipated duration of the underlying disease, and any potential medical issues that could complicate pharmacotherapy. Insomnia therapy should be directed to preserve the quality of daytime function, improving sleep with a minimum of

residual cognitive dulling, lingering hypnotic effects, or uncomfortable side effects. There may be a role for medications that have antidepressant or anxiolytic characteristics, especially in the early stages following cancer diagnosis. Chronic treatment may be better achieved by nonpharmacologic interventions *(54,55)* such as cognitive therapy, relaxation therapy, biofeedback, and behavioral approaches to improve sleep quality.

Degenerative conditions of the CNS alter the chemical and structural substrates that regulate sleep; most of these produce fragmented sleep, with or without daytime hypersomnia. Disrupted sleep patterns are common in Alzheimer's Dementia *(56)*, and the difficulties produced by perceptual impairment may aggravate nocturnal behaviors and confusion *(57,58)*, characterized as a "sundown" syndrome. Cholinergic agonists or cholinesterase inhibitors utilized to treat Alzheimer's Dementia may aggravate difficulties with sleep initiation, by augmenting cholinergic tone in the basal forebrain and cerebral cortex, favoring the maintenance of wakefulness. Parkinson's disease (PD) may disrupt sleep by way of tremor, dystonia, or periodic nocturnal movements, whereas the dopamine agonist medications used for treatment of PD may also cause insomnia, dystonia, or dyskinesia. Thus, inadequate symptomatic treatment at night or the side effects of treatment may cause sleep disruption by similar mechanisms. The dopamine agonists tend to enhance dreaming, and many patients report increased nightmares in association with bedtime doses of levodopa and pergolide. These medications may also cause increased motor activity during dreams. Lewy body dementia has a high incidence of REM behavior disorder and sleep fragmentation *(58a)*. The EEG in progressive supranuclear palsy has been observed to include more elemental changes in sleep architecture, with decreased total sleep time, decreased sleep spindles, and diminished REM sleep *(59,60)*. Multiple systems atrophy also produces considerable sleep disruption, with increased arousal and diminished slow wave sleep *(61)*. Huntington's chorea has been associated with decreased sleep efficiency, and sleep may become dramatically fragmented as behavioral symptoms increase. Fatal Familial Insomnia is a rare prion-associated spongeform encephalopathy with rapid progression through fulminant insomnia to dementia and death over the course of months *(62)*. Insomnia is also commonly seen in association with Creutzfeldt-Jakob disease *(63,64)*, especially when the thalamic degeneration is disproportionately observed.

Neuropathy and radiculopathy are associated with chronic pain, fasciculations, and muscle spasms that cause impaired sleep initiation/maintenance, and periodic limb movements of sleep are augmented in peripheral nerve disorders, further exacerbating difficulties with sleep maintenance. Muscular dystrophy and inflammatory myopathies can cause insomnia by similar mechanisms, in addition to their effects on ventilatory and pharyngeal musculature that lead to hypoventilation and frequent aspiration. Most of the medications used to treat the symptoms of neuropathy are sedating for the majority of people who take them, but the anticonvulsants carbamazepine and lamotrigine have been reported to cause insomnia. Myelopathy can also cause pain, muscle spasms, spasticity, constipation,

Table 1
Causes of Secondary Insomnia

Skin conditions
Allergic, infectious, or inflammatory dermatitis
Burns
Herpes zoster reactivation (shingles)
Lacerations
Swelling
Edema
Diaphoresis
Dressings, bandages, or splints
Oral corticosteroid medications
Sleep-disordered breathing due to pathology in the nasopharynx, oropharynx, and larynx
Nasal polyps
Excessive oropharyngeal adipose tissue
Oropharyngeal or nasopharyngeal mass lesion
Macroglossia
Uvular hypertrophy
Retrognathia
Pharyngeal muscle weakness
Neck anatomy (short, broad, restricted in motion, anterior adipose deposition)
Cervical mass lesions
Hyoid pathology
Cervical spine degeneration
Other conditions affecting the pharyngeal and laryngeal tree
Postnasal drip
Chronic/recurrent sinusitis
Allergic, infectious, or inflammatory pharyngitis
Sleep-related laryngospasm, choking, or repetitive swallowing
Bruxism
Pulmonary disorders
Asthma
Chronic obstructive pulmonary disease
Restrictive/interstitial pulmonary disease
Bronchitis
Pneumonia/pneumonitis
Pleuritis
Pulmonary neoplasia
Hypoxia
Chest wall pain
Cough
Bronchodilator medications, methylxanthines derivatives, inhaled steroids
Cardiovascular diseases
Nocturnal angina
Ppalpitations, tachycardia, arrythmia
Paroxysmal dyspnea
Orthopnea

Table 1 (continued)

- Congestive heart failure
- Myocardial infarction
- Vasodilating medications
- Digoxin
- Diuretics

Disorders of the gastrointestinal system
- Gastroesophageal reflux disorder
- Gastric and peptic ulcer disease
- Infectious, inflammatory, allergic intestinal disorders
- Neoplasia of the gastrointestinal tract
- Milk allergy/food allergies

Urological disorders
- Prostatic hypertrophy
- Prostatic carcinoma
- Prostatitis
- Interstitial cystitis
- Bladder infection
- Nephrolithiasis
- Neurogenic bladder
- Chronic renal disease
- Hemodialysis

Rheumatoid/musculoskeletal disorders
- Rheumatoid arthritis
- Ankylosing spondylitis
- Systemic lupus erythematosis
- Vasculitis
- Polymyalgia rheumatica
- Fibromyalgia
- Pain
- Chronic fatigue syndrome
- Osteoarthritis
- Degenerative change of the spine
- Scoliosis
- Scleroderma

Endocrine changes
- Hyperthyroidism
- Hypothyroidism
- Adrenal dysfunction
- Menses
- Menopause
- Diabetes mellitus

Pregnancy

Neoplastic or hematologic disorders

Disorders of the nervous system
- Alzheimer’s dementia
- Parkinson’s disease

(continued)

Table 1 (continued)

Lewy body dementia
Progressive supranuclear palsy
Multiple systems atrophy
Huntington's disease
Fatal Familial Insomnia
Creutzfeldt-Jakob disease
Neuropathy/radiculopathy
Muscular dystrophy
Inflammatory myopathy
Myelopathy
Amyotrophic lateral sclerosis
Stroke
Multiple sclerosis
Antoparkinsonian medications
Cholinergic agonists
Interferon therapy
Cerebral mass lesions
Cerebral palsy
Headache
Head injury
Encephalitis/meningitis (including Lyme disease and HIV)
Epileptic syndromes

and bladder dysfunction that contribute to secondary insomnia. Restriction of body movement by severe neuropathy or myelopathy can cause discomfort due to the development of soreness over bony prominences, pressure sores, or arthralgia due to malpositioned extremities. For this reason, insomnia becomes especially prominent with the symptomatic progression of amyotrophic lateral sclerosis, worsening as bulbar involvement becomes prevalent *(65)*.

Stroke can produce impaired sleep due to structural changes in the cerebrum *(56,66)*, especially when ischemia has affected the thalamus, anterior hypothalamus, or the central pons *(67)*. A stroke can also produce insomnia by way of its associated physical symptoms, such as movement restriction due to paresis, sensory disruption causing parasthesia/dysesthesia, or impaired pharyngeal function causing aspiration and obstructive breathing. Multiple sclerosis may cause insomnia as demyelinated plaques involve more of the cortical mantle or the diencephalon, and may also be aggravated by motor, sensory, or urological symptoms that increase with the progression of the disease. Insomnia has also been reported with various forms of interferon therapy *(68)*. It has been seen with lesions involving the pituitary *(69)* and pineal gland *(70)*. Cerebral palsy may significantly affect sleep

architecture *(71)*, and assessment by PSG may be made difficult by the significant EEG alterations seen with more severe structural abnormalities in the brain.

Headache may occur during sleep, as in the syndromes of cluster headache *(72)*, paroxysmal hemicrania, and migraine headache, producing significant sleep disruption *(73)*. These headache types may appear intermittently or in occasional flurries of several nights, and are less often associated with chronic insomnia. The rebound headache caused by analgesic overuse, drug abuse, or drug withdrawal is more likely to cause chronic problems with awakening that impairs the quality of sleep *(74)*. Nocturnal headache may also reflect sleep-related pathology such as bruxism or sleep apnea *(75)*. Acute head injury typically produces hypersomnia, gradually changing to insomnia over the course of weeks to months. Milder head trauma may produce chronic insomnia of disproportionate character *(76)*, typically accompanied by a variety of somatic symptoms. Meningitis and encephalitis may cause acute and chronic changes in sleep quality. The acute phase of an encephalitic process may produce symptoms ranging from hypersomnia to agitation and delirium. After the resolution of acute infection, insomnia is a common sequela *(77)*. Insomnia may also be seen in paraneoplastic encephalitis *(78)*. Insomnia may be seen following CNS involvement in Lyme disease *(79)*, and is common in chronic HIV infection *(80)*.

Epileptic syndromes may include nocturnal seizures of sufficient frequency to cause sleep disruption, and cumulative sleep disruption may in turn increase the frequency of seizures. Studies have shown that up to 45% of people with epilepsy have their seizures mostly during the night *(81)*. Autosomal-dominant frontal lobe epilepsy, lesional frontal lobe epilepsy, benign partial epilepsy with centrotemporal spikes (Benign Rolandic Epilepsy), and electrical status epilepticus of sleep produce seizures that occur mostly during sleep. Juvenile myoclonic epilepsy, temporal lobe epilepsy, and symptomatic generalized epilepsy (Lennox-Gastaut Syndrome) may include seizures that predominate during sleep. Sleep architecture in epilepsy may be disturbed even on nights without seizure activity, as shown in a cohort of patients with temporal lobe epilepsy compared to normal controls *(82)*. Changes in sleep architecture may include decreased total sleep time, decreased sleep efficiency, increased arousals, increased WASO, and reduced REM sleep. Of the anticonvulsant medications, insomnia has been reported most often with membrane-stabilizing agents including phenytoin, carbamazepine, oxcarbazepine, lamotrigine, and felbatol. Anticonvulsant medications that enhance GABA tone in the CNS, such as barbiturates, benzodiazepines, valproic acid, tiagabine, gabapentin, and vigabatrin, are less likely to cause insomnia. Studies of sleep architecture during anticonvulsant therapy have shown a broad range of effects, including a reduction in slow wave sleep and an increase in stages 1 and 2 of NREM sleep *(83)* during chronic treatment. Some studies have shown contradictory effects, and there has been little correlation of sleep effects with anticonvulsant drug levels. Overall, the sleep-related benefits of improved seizure control may outweigh any negative influence the anticonvulsant medications might have on sleep *(84)*.

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11

Insomnia in Psychiatric Disorders

Samy S. Karaz

The best bridge between despair and hope is a good night's sleep

—E. Joseph Cossman

INTRODUCTION

Management of insomnia without a basic understanding of the possible underlying psychiatric disorders might result in an inadequate, if not hazardous outcome. Insomnia is listed in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) as a symptom of several psychiatric disorders (*see* Table 1) *(1)*.

Insomnia related to other *DSM-IV* mental disorders was found to be as high as 77%. In more than 50% of the cases, the diagnosis was a depressive disorder *(2)*.

In general, 57% of individuals reporting insomnia have a psychiatric disorder or will develop one within a year *(3)*. Second to depression, anxiety disorders are strongly associated with insomnia.

SLEEP AND DEPRESSIVE DISORDERS

Patients with major depressive disorders present with depressed mood or loss of interest or pleasure.

The full *DSM-IV* criteria of major depression are listed in Table 2 *(4)*.

The most characteristic feature of insomnia seen in major depression is repeated awakenings leading to early morning or "premature" insomnia. Waking up early and not being able to return to sleep is a cardinal complaint *(5)*. Younger depressed patients might present with initial insomnia. The most characteristic sleep-tracing (polysomnographic) features of major depression is earlier onset of the first rapid eye movement (REM) period. Other abnormalities include reduced delta sleep and increased REM sleep *(5)*. The severity of insomnia correlates with the severity of depression. Despite the overwhelming evidence of insomnia and sleep architecture abnormalities, patients with major depression do not usually present with symp-

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Table 1
***DSM–IV* Diagnoses with Insomnia as a Symptom**

Diagnosis	*DSM-IV* Criteria
Separation anxiety disorder	Reluctance or refusal to go to sleep without being near a major attachment figure and repeated nightmares involving the theme of separation.
Alcohol withdrawal	Insomnia
Stimulant withdrawal (including cocaine, amphetamines, nicotine or caffeine)	Insomnia or hypersomnia
Sedative withdrawal (including opiates, hypnotics, anxiolytics, and antidepressants)	Insomnia
Major depression	Insomnia or hypersomnia every day
Dysthymia	Insomnia or hypersomnia
Posttraumatic stress disorder	Recurrent distressing dreams of the traumatic event leading to difficulty falling or staying asleep.
Acute stress disorder	Reexperiencing the trauma in recurrent nightmares
Generalized anxiety disorder	Insomnia
Primary insomnia	The predominant complaint is difficulty initiating or maintaining sleep or nonrestorative sleep, for at least 1 month.
Nightmares	Repeated awakening from any sleep period due to frightening and vivid dreams
Sleep terrors	Recurrent episodes of abrupt awakening from sleep, usually occurring during the first third of the major sleep episode.
Sleep disorder due to another psychiatric disorder	Insomnia due to the other psychiatric disorder
Sleep disorder due to another medical condition	Insomnia due to other medical disorder
Postconcussional disorder	Insomnia or hypersomnia
Premenstrual dysphoric disorder	Insomnia or hypersomnia

Adapted from ref. *1*.

toms of excessive daytime sleepiness. Patients with major depression frequently present with symptoms of tiredness and lack of energy. Accordingly, it is of clinical importance to try to differentiate between tiredness with a lack of energy and excessive daytime sleepiness in patients with insomnia. On the other hand, as a part of bipolar disorder and seasonal affective disorder, depression is usually accompanied by increased sleep efficiency, frequent napping, and daytime sleepiness *(5)*.

In hypomanic or manic phase of bipolar disorder, patients usually sleep as little as 2 to 4 hours each night, yet they wake up feeling subjectively refreshed. The

Table 2
Diagnostic Criteria for a Major Depressive Episode

In the same 2 weeks, the patient has had five or more of the following symptoms, which are a definite change from usual functioning. Either depressed mood or decreased interest or pleasure must be one of the five.

- Depressed mood for almost all day nearly every day
- Markedly decreased interests for almost all day nearly every day.
- Appetite and or weight increased or decreased for almost all day nearly every day.
- Decreased or increased sleep for almost all day nearly every day.
- Patient agitated or retarded for almost all day nearly every day.
- Fatigue or loss of energy for almost all day nearly every day.
- Patient feels worthless or inappropriately guilty for almost all day nearly every day.
- Trouble thinking or concentrating for almost all day nearly every day.
- Repeated thoughts about death (other than the fear of dying), suicide (with or without a plan), or has made a suicide attempt.

These symptoms cause clinically important distress or impair work, social, or personal functioning

This disorder is not directly caused by a general medical condition or the use of substances, including prescription medications.

Unless the symptoms are severe (defined as severely impaired functioning, severe preoccupation with worthlessness, ideas of suicide, delusions, or hallucinations, or psychomotor retardation), the episode has not begun within 2 months of the loss of a loved one.

absence of depression symptoms in the initial evaluation of insomnia should not rule out the risk of major depression in future visits. Patients with insomnia and no depression at intake were at approximately 40-fold higher risk of developing new episodes of major depression in comparison to individuals with no insomnia *(6)*. There is another group of insomnia patients who have major depression, yet their sole complaint is insomnia. The psychiatric literature described individuals with "Alexithymia" (patients without words to express their feeling state). These individuals are more likely to have "masked depression." They are particularly commonly seen in the primary care setting. Patients with masked depression substitute somatic complaints such as insomnia for the traditional core symptoms of depressed mood or loss of pleasure.

Therefore, it is important to focus on the objective component of the mental status.

The general demeanor and posture of patients with depression may appear to be slowed. They may walk slowly, holding their heads down and lacking spontaneity. Patients with depression may respond to questions with long pauses and short answers *(7)*. Their facial expressions may be blunted and their eye contact may be

poor. Focusing only on the contents of the patient's complaints may result in overlooking depression and in turn a poor treatment outcome. Severe insomnia is an independent risk factor for suicide during the first 2 years of an episode of major depression *(8)*.

Treatment of Depression/Insomnia Symptoms

Selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, paroxetine, sertraline, and fluvoxamine are commonly used for treatment of depression. SSRI antidepressants decrease total sleep time (TST), increase number of arousals, suppress REM sleep, and increase the number of phasic REMs. Despite their arousing effect on the sleep electroencephalogram (EEG), SSRI antidepressants improve subjective sleep quality in subjects with major depression and primary insomnia *(9)*. On the other hand, insomnia is the most common residual symptom among patients who have otherwise been successfully treated with fluoxetine for depression. This phenomenon may be unique to the newer antidepressant medications like fluoxetine *(8)*.

Tricyclic antidepressants play a role in treatment of depression/anxiety symptoms. Tricyclic antidepressants decrease REM sleep and increase REM latency. EEG measures of sleep continuity may improve with tricyclic antidepressants *(8)*.

The tertiary amine tricyclic antidepressants (e.g., Amitriptyline and Imipramine) have a more sedating effect than the secondary amine tricyclics like Desipramine and Nortriptyline. The secondary amines group has fewer adverse effects. Some clinicians believe that depressed patients with marked insomnia and anxiety obtain some immediate relief from the sedating antidepressants before the full antidepressant effect takes place, which might increase the likelihood of compliance during the acute phase of treatment *(10)*.

One drawback of the tricyclic antidepressants is the risk of fatal effects if an overdose is ingested. Patients were randomly assigned to an initial prescription of the SSRI fluoxetine or the tricyclic Imipramine. The rate of improvement in insomnia was identical in both groups *(11)*. Serotonin receptor modulators like Trazodone and Nefazodone increase sleep continuity. However, Trazodone decreases REM sleep and may cause daytime sedation, whereas Nefazodone increases REM and has minimal daytime sedation *(12)*.

Monoamine oxidase inhibitors (MAOIs), antidepressants like Tranylcypromine (Parnate) and Phenelzine (Nardil), still have a role in the treatment of depression. However, because of the necessity to regulate the diet and to continuously evaluate the concomitant medications, MAOIs are not used as a first line of treatment *(10)*.

Benzodiazepines like Lorazepam, Clonazepam, and Alprazolam are sedating, induce sleep, and have anti-anxiety and muscle relaxant effects. Newer medications like Zolpidem act selectively on the ω_1 benzodiazepine receptors and have a sedative effect without anxiolytic, anticonvulsant, and muscle relaxant effects. They do not cause rebound effects or withdrawal when discontinued *(12)*. A double-blind study by Smith and co-workers found that patients taking fluoxetine for

depression showed greater improvement in their psychiatric symptoms when taking Clonazepam concomitantly *(12)*. In a double-blind study by Rosenberg et al., Zolpidem was found to improve the quantity and quality of sleep without worsening depression when co-administered with antidepressants *(12)*. Patient's individual susceptibility to certain side effects, personal and family history of previous response to specific antidepressants, history of alcohol or drug abuse, patient's age, and possible other concomitant underlying medical problems should all be factored in when an antidepressant and/or benzodiazepine are to be selected.

Case 1

A 45-year-old married male was referred to the sleep center by his primary care physician.

The patient presented with symptoms of frequent awakening and poor night's sleep.

He went to bed at 10:30 PM and was able to fall asleep within 15 to 20 minutes. Two to three hours later, he would wake up for a brief period of time and would fall asleep again for several minutes. He would repeat the pattern a few times before waking up between 3:30 and 4:00 AM, at which time he would be unable to fall asleep for the rest of the night. He would stay in bed tossing and turning and then get out of bed at 6 AM. He reported that his symptoms started 3 months previously. He complained of feeling tired, yet denied any symptoms of excessive daytime sleepiness.

He reported that his job as a banker started to become more stressful 6 months previously.

He did not drink alcohol and smoked 15 cigarettes a day. He has been a smoker since age 18. He reported that he would smoke one or two cigarettes at night when he could not sleep. He was unaware of any positive family history of sleep disorders. He had a history of arthritic low back pain and high cholesterol. He denied any past psychiatric history.

On physical exam, chest exam showed scattered rhonchi bilaterally and the patient had some productive cough. Otherwise, physical exam was essentially normal.

At the end of this visit, the patient was given educational material on sleep hygiene and insomnia. Behavioral techniques like stimulus control therapy and relaxation were discussed.

He was started on 1 mg of Lorazepam orally at bedtime. The patient did not call between visits to report his progress although he was advised to do so.

On the second visit, 4 weeks later, the patient was apologetic. He admitted to feeling guilty for not complying with the behavioral treatment recommendations. He reported that he was not waking up as much during the night on Lorazepam, yet he complained of ongoing difficulties waking up early in the morning and feeling more tired during the day.

He felt hopeless that his sleep would improve. His eye contact was poor, and his affect appeared dysthymic. He admitted to loss of interest and to isolating himself socially. He admitted to having brief death wishes, yet denied any specific suicidal ideations or plans.

The patient was informed that he meets the diagnosis of major depression and was started on 20 mg of fluoxetine orally in the morning. He was continued on 1 mg of Lorazepam orally at bedtime.

On the third visit, 4 weeks later, the patient's affect was brighter and he reported that he was less tired and his sleep was improving. He also reported improvement of his mood and level of interest. He denied any death wishes or thoughts of suicide. He felt more hopeful. He was continued on the same dose of fluoxetine and Lorazepam was switched to 1 mg at bedtime on an as needed basis.

On the fourth visit, 6 weeks later, he was free of symptoms of depression and insomnia. Lorazepam was infrequently used and accordingly, it was gradually tapered and then discontinued. He continued on the same dose of fluoxetine.

INSOMNIA AND ANXIETY DISORDERS

Sixteen million Americans suffer from anxiety disorders *(13)*. The interrelationship between anxiety disorders and insomnia is a very common finding in the clinical setting. Anxiety and related conditions (tension, psychic distress) were found to be quite prevalent among insomniacs in epidemiological studies of either the general population or the elderly. The vast majority of insomniacs manifested the symptoms of apprehension, rumination, multiple fears, and excessive worrying *(14)*.

Generalized Anxiety Disorder

Patients with generalized anxiety disorders (GADs) experience chronic and persistent anxiety and, not surprisingly, most report problems with insomnia *(15)*. Fifty to seventy percent of patients with GAD report trouble sleeping *(16)*. Sleep disturbance is characterized by sleep-onset or maintenance insomnia due to excessive anxiety and apprehensive expectations about one or more life circumstances. These patients may express intense anxiety during the daytime about the inevitability of each night's poor sleep. Patients display chronic anxiety with features that include trembling, muscle tension, restlessness, easy fatigability, shortness of breath, palpitations, tremors, sweating, dry mouth, dizziness, keyed up feelings, and exaggerated startle response *(5)*.

The *DSM-IV* criteria of GAD is listed in Table 3 *(4)*.

The polysomnographic features of GAD reveal the nonspecific findings of increased sleep latency (SL), decreased sleep efficiency, increased amount of stage 1 and stage 2 sleep and decreased slow wave sleep. These changes are often mild. There is usually little to no physiologic sleepiness on the Multiple Sleep Latency

Table 3
Diagnostic Criteria for Generalized Anxiety Disorder

Worries and anxieties over several events and activities for 50% of the time or more for at least 6 months.

The person experiences difficulty or trouble trying to control these feelings.

In addition to the above there are at least three of the symptoms listed below for 50% of the time or more for at least 6 months.

- Feels restless, edgy, keyed up
- Tires easily
- Trouble concentrating
- Irritability
- Increased muscle tension
- Trouble sleeping (initial insomnia or restless, unrefreshing sleep)

The cause of the anxiety and the worry is not an aspect of another psychiatric illness.

The anxiety is not the symptom of another medical condition.

The anxiety is not the symptom of another psychiatric condition.

The symptoms cause clinically important distress or impair work, social, or personal functioning.

Test of patients with GAD *(4)*. There are similarities between psychophysiologic insomnia and GAD in both their clinical presentation and the polysomnographic changes.

If anxiety permeates most aspects of functioning, a GAD is the usual diagnosis. In contrast, if anxiety is focused almost exclusively on poor sleep and its consequences on daytime functioning, psychophysiologic insomnia is the typical diagnosis *(17)*.

On the other hand, patients with GAD experience pervasive anxiety during the day, which interferes with their level of functioning well beyond the consequences of poor sleep *(10)*.

In contrast with GAD, sleep efficiency improves on the second night in patients with psychophysiologic insomnia when their nighttime sleep polysomnogram (PSG) is recorded in the sleep lab 2 nights in a row *(4)*.

Treatment

Benzodiazepines like Alprazolam and Clonazepam continue to play a major role in the management of GAD. SSRI antidepressant medications like fluoxetine, paroxetine, sertraline, and a tricyclic antidepressant like Imipramine are found to be valuable options in the treatment of GAD. Cognitive-behavioral therapy should be strongly considered as an important tool in the treatment of GAD and the related insomnia.

Table 4
Diagnostic Criteria for Panic Disorder

The patient suddenly develops a severe fear or discomfort that peaks within 10 minutes.

During this discrete episode, four or more of the following symptoms occur:

- Choking sensation
- Chills or hot flashes
- Chest pain or other chest discomfort
- Fear of dying
- Dizzy, lightheaded, faint, or unsteady
- Derealization (feeling unreal) or depersonalization (feeling detached from self)
- Fears of loss of control or becoming insane
- Heart pounds, races, or skips beats
- Nausea or other abdominal discomfort
- Numbness or tingling
- Sweating
- Shortness of breath or smothering sensation
- Trembling

Panic Disorder

Sleep disturbances have been reported in 70% of patient's with panic disorder *(18)*. The panic attack is characterized by a sudden, intense fear or terror of dying. Symptoms include dizziness, choking, palpitation, trembling, chest pain, or discomfort, and sweating *(4)*.

Symptoms of panic attack as listed in the *DSM-IV* is shown in Table 4.

Panic disorder can be associated with sudden awakening from sleep. Nocturnal panic attacks present with similar symptoms to daytime panic. Palpitation, dyspnea, and flushing are the most frequent symptoms of nocturnal panic attacks *(18)*. Polysomnographic monitoring of nocturnal panic demonstrates an abrupt awakening with a sensation of panic out of stage 2 or 3 sleep. It also presents with marginally increased SL and decreased sleep efficiency.

Obstructive sleep apnea (OSA) may lead to awakening with panic-like symptoms. OSA usually presents with symptoms of snoring, sleepiness, and the absence of daytime anxiety, which distinguishes OSA from panic disorder *(4)*.

Night terrors, which also emerge from non-rapid eye movement (NREM) sleep are usually followed by no recollection of the events and there is no daytime panic symptoms. Nightmares differ from panic attacks as they usually cluster around the early morning and contain much more mental content *(4)*.

It is important to note that panic disorder is associated with major depression in 50 to 94% of patients *(18)*. This comorbidity could result in alteration of the presentation of insomnia symptoms.

Treatment

SSRI antidepressants like paroxetine, fluoxetine, sertraline, fluvoxamine, or citalopram are the current consensus to start treating a patient with uncomplicated panic. Many patients with panic disorder have what is described as supersensitivity syndrome, which is an initial agitation and more frequent panic in the first 1 to 2 weeks of starting an SSRI medication. Further reduction of the dosage adding benzodiazepine, or switching to a different compound from the same family usually gets the patient through this relatively short period *(10)*.

Benzodiazepines are powerful anti-panic drugs. The major advantage of benzodiazepines is their quick onset of action. Follow-up studies suggest that benzodiazepine-responsive patients maintain their gain for several years and do not develop tolerance. Maintenance doses are usually lower than the dosages used for acute treatment *(10)*.

MAOIs are potent anti-panic drugs, yet their use is limited by the necessity to regulate the diet and continuously evaluate the concomitant medications.

Tricyclic antidepressants, particularly Imipramine and Clomipramine, are very effective anti-panic medications.

Case 2

A 30-year-old single female was seen in the sleep center for symptoms of difficulty initiating and maintaining sleep. She complained that her insomnia symptoms started 1 year ago, yet it worsened in the previous 3 months. She worked as a school teacher. The new school year started 2 months prior to her visit. She admitted to lying in bed at night awake worrying about what might go wrong at school. She went to bed at 10 PM. She stayed awake for a couple of hours tossing, turning, and worrying. She woke up two to three times at night and at least once she was up for about an hour. She glanced at the clock and worried about not being able to fall asleep. She got up at 6 AM and usually did not need an alarm.

She felt tired during the day, yet denied sleepiness behind the wheel or at any time when physically inactive. She denied being able to take naps. The patient did not smoke and seldom drank alcoholic beverages.

She denied any history of a psychiatric disorder. She reported a history of a knee injury while jogging and denied any other medical problems. Physical exam was essentially normal.

During the evaluation, the patient appeared tense and her voice was shaky. In the latter part of the visit and while discussing the treatment plan, the patient appeared more anxious and was tremulous. She had increasing difficulty focusing on the conversation.

When the patient's anxiety signs were addressed, she reported that her anxiety symptoms date back to at least 5 to 6 years ago if not longer. She

complained of feeling anxious during the day and not only at night. She admitted to always worrying about what might end up going wrong. She complained of feeling tired and not being able to control or stop these anxious thoughts. She complained of always feeling keyed up. The patient appeared to meet the criteria of GAD, as well as insomnia. She was educated regarding the nature of her anxiety and the treatment plan was altered in order to treat her anxiety disorder symptoms as well as insomnia. She was referred for cognitive-behavioral therapy sessions with focus on relaxation training, and worry reduction. She was started initially on .5 mg of Klonopin orally at bedtime, which was increased to 1 mg at bedtime.

Six weeks later, during the second visit, the patient reported significant improvement of both her anxiety and nighttime sleep. She was able to successfully utilize the relaxation techniques. Klonopin was decreased down to .5 mg at bedtime.

The patient reported later on that she was able to maintain solid sleep on the lower dose of Klonopin in combination with utilizing the cognitive and behavioral therapy techniques. The patient tried to stop Klonopin completely, yet she experienced difficulties with some sleep fragmentation and resumed the dose of .5 mg at bedtime.

Posttraumatic Stress Disorder

Insomnia and nightmares are common symptoms of posttraumatic stress disorder (PTSD). Of patients with PTSD or individuals exposed to major stress, 59–68% report frequent nightmares *(16)*. Insomnia is part of the hyperarousal complex of symptoms and nightmares are characteristic in the symptoms cluster of reliving the traumatic events *(19)*. The anxiety arousals in PTSD may emerge from both REM-related nightmares and may also arise from NREM sleep *(16)*. Cognitive-behavioral therapy for nightmares and insomnia was associated with improvement of the symptoms of PTSD *(20)*. SSRI antidepressants have also proven to be effective in the treatment of PTSD and insomnia. Fluvoxamine was found to be effective, particularly in the treatment of traumatic-related nightmares and sleep maintenance insomnia *(9)*.

Trazodone was also found to be effective in the treatment of nightmares and insomnia associated with PTSD *(19)*. Benzodiazepines and tricyclic antidepressants were also found to be effective in the treatment of PTSD.

OTHER DISORDERS

Other anxiety disorders (e.g., obsessive-compulsive disorder) and other psychiatric disorders (e.g., schizophrenia, eating disorders, dementia, and alcoholism) are accompanied by problems with insomnia and sleep architecture changes. Details of these changes are illustrated on Table 5 *(15)*.

Table 5
Sleep Abnormalities in Psychiatric Disorders

Disorder	Symptoms	Objective findings
Major depression	Insomnia, vivid dreams, nightmares, and fatigue	↓total sleep ↑sleep latency ↓sleep efficiency ↑wake time ↑REM
Seasonal affective disorder/ bipolar depression	Hypersomnia	↑total sleep time
Mania	Insomnia	↓total sleep ↑sleep latency ↓sleep efficiency ↑wake time ↑REM
Anxiety disorders	Insomnia	↓ sleep continuity
Posttraumatic stress disorder	Insomnia, flashback dreams	Normal or ↑REM
Schizophrenia	Insomnia, reversal of sleep wake cycles	↓ sleep continuity, normal or ↓SWS, normal or ↓REM sleep
Eating disorders	Insomnia, sleep-related eating spells	Normal or ↓ sleep continuity, normal or ↓REM sleep
Alcoholism	Insomnia	↓ sleep continuity, ↓SWS, normal or ↓REM sleep, normal or ↑REM %
Dementia Alzheimer's type	Insomnia, reversal of sleep–wake cycles	↓total sleep ↑sleep latency ↑wake time, ↓SWS.

Adapted from ref. *15*.
REM, rapid eye movement; SWS, slow-wave sleep

Insomnia and Substance Abuse

Alcoholism

Special attention needs to be given to alcoholism, as it is often associated with anxiety disorders, depression, and insomnia. Acute alcohol use reduces the amount of wakefulness for the first 3 to 4 hours of sleep. The amount of wakefulness increases during the second half of the night and sometimes the number of dreams, particularly anxiety dreams, increase.

Chronic, excessive alcohol use eventually results in fragmented and restless sleep *(5)*.

Sleep problems due to alcohol abuse could be confused with insomnia due to psychiatric disorders or primary insomnia if the problem with alcoholism is overlooked or not addressed.

It is advisable to avoid prescribing benzodiazepines if alcohol use is a problem. Benzodiazepine-prescribing decisions vary widely among physicians. Although some agreed with prescribing for patients with high probability of alcohol abuse,

other physicians avoided benzodiazepines unnecessarily, depriving certain insomnia patients from a viable treatment option *(21)*.

Caffeine

Caffeine is a stimulant that is consumed in coffee (85 mg–150 mg per cup), tea (60–75 mg per cup), cocoa (50 mg per cup), chocolate, over-the-counter (OTC) cold preparations (15 mg–60 mg per tablet), and OTC stimulants (100–200 mg).

Caffeine effects may last for 8 to 14 hours. Caffeine consumption might induce or worsen insomnia, even if it is consumed as early as the late afternoon.

For most people, 1 g of caffeine may induce insomnia. Other more sensitive individuals may become overstimulated on as little as 250 mg *(16)*.

The polysomnography changes with caffeine shows increased SL, decreased TST, increased wake after sleep onset (WASO), decreased REM sleep, and decreased delta sleep *(22)*.

Nicotine

Nicotine can be consumed by smoking, chewing tobacco, snuff, nicotine patches, and nicotine gum. Nicotine is addictive. Withdrawal from nicotine starts 1 to 2 hours after the last smoke *(16)*. Abrupt cessation or decrease of the nicotine consumption can result in insomnia in the following 24 hours *(4)*. Cigarette smoking accelerates the metabolism of certain medications including Diazepam, Lorazepam, Oxazepam, and Imipramine. This could result in a decrease of the sedative effect of these medications among smokers. Nicotine polysomnography changes include increased SL, decreased TST, and decreased REM sleep *(22)*.

Stimulants

Amphetamines such as methamphetamine "speed" are taken intravenously, by snorting, or by smoking "ice." PSG changes on amphetamines are decreased TST, increased WASO, increased movement during sleep, decreased REM sleep, and decreased delta sleep *(22)*.

Cocaine is also taken intravenously, by snorting, or smoking (as free base "crack").

PSG changes on cocaine are increased SL, decreased TST, and decreased REM sleep *(22)*.

Serious medical and psychiatric complications result from stimulant abuse and among these complications are a disruption of the sleep–wake pattern and insomnia. Stimulants (e.g., amphetamines and methylphenidate) are used therapeutically in the treatment of narcolepsy, attention deficit hyperactivity disorder, some causes of depression, and other related disorders. The availability of objective diagnostic tools and careful clinical monitoring helps decrease the risk of stimulant abuse among these patients population.

Anxiolytics and Sedative Hypnotics

The present major anxiolytics and sedative hypnotics include benzodiazepine and other miscellaneous drugs (Zolpidem, Chloral Hydrate, and Zalpelon) *(16)*.

The older sedative hypnotics like barbiturates are less frequently used due to the higher risk of dependence and the more severe withdrawal symptoms like withdrawal seizures.

The benzodiazepines polysomnographic changes include increased TST, decreased WASO, decreased REM sleep, and increased sleep spindles in stage 2. Most benzodiazepines decrease the SL and decrease delta sleep *(22)*.

The sedative hypnotics abuse occurs predominantly in the context of polysubstance abuse *(16)*. Benzodiazepines with rapid onset of action (e.g., Alprazolam and Diazepam) are more likely to be abused than the longer onset of action type of benzodiazepine (Oxazepam or Chlordiazepoxide). Withdrawal from sedative hypnotics can result in a rebound insomnia or emergence of insomnia as a new symptom (in prolonged high-dose use). Anxiety is a common withdrawal symptom, which independently can initiate or worsen insomnia. In evaluating the risks vs benefits of the sedative hypnotic therapy in patients including those who have insomnia, it is helpful to distinguish between "drug-seeking behavior" from "therapy-seeking behavior" *(16)*.

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12

Insomnia in Primary Sleep Disorders

Stephen Duntley

DEFINITION

Insomnia is defined in the *International Classification of Sleep Disorders* as "difficulty in initiating and/or maintaining sleep" *(1)*. In primary insomnia, the term *insomnia* constitutes a diagnostic entity. In other disorders it is considered a symptom and not a primary diagnosis. Insomnia is frequently a component of the symptom complexes of other primary sleep disorders, and is listed among the diagnostic criteria for the following dyssomnias: obstructive sleep apnea (OSA) syndrome, central sleep apnea syndrome, central alveolar hypoventilation syndrome, periodic limb movement disorder (PLMD), and restless legs syndrome (RLS). Disrupted sleep is among the diagnostic criteria for narcolepsy. The complaint of insomnia can also accompany parasomnias, and is listed among the diagnostic criteria for sleep starts and nightmares *(1)*. As in other forms of insomnia, in order to be considered a clinically significant problem, the complaint of sleep disturbance must be associated with adverse daytime consequences such as fatigue, decreased concentration, or irritability.

HISTORICAL PERSPECTIVES

In what is likely the first report of RLS in the medical literature, Thomas Willis, an English physician, described a patient in the late 1600s for whom sleep was impossible because of restlessness in the arms and legs, which were compared to a person being tortured on the rack. There were subsequently sporadic reports of patients with similar symptoms, but the syndrome was not described in detail until the 1940s. A thorough description of the phenomenon of PLMs during sleep awaited development and clinical application of polysomnography, with typical features being described by Lugaresi and colleagues in 1966 *(2)*. Insomnia associated with OSA was first described by Guilleminault and colleagues in 1973 *(3)*. Since these initial reports, the common association between insomnia and these other sleep

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disorders has been confirmed, although the clinical significance of this relationship continues to be defined.

EPIDEMIOLOGY

The epidemiology of insomnia in sleep disorders is dependent on the epidemiology of the primary sleep disorder itself. One community-based population study found about 2% of women and 4% of men have OSA syndrome *(4)*. A recent university-based study of patients with sleep-disordered breathing found that of 231 patients sampled, 116 complained of clinically significant insomnia *(5)*. Among postmenopausal women complaining of insomnia, 83% were noted to have upper airway resistance syndrome (UARS) or OSA syndrome *(6)*. Insomnia complaints in patients with OSA syndrome, like insomnia complaints in general, may be more frequent among women than men *(7)*. Central sleep apnea syndrome is less common than OSA, but patients appear to be less likely to report daytime hypersomnolence and more likely to complain of insomnia *(8)*. RLS is common, with a recent population-based study revealing bedtime symptoms in 10–15% of individuals *(9)*. Difficulty falling asleep was reported by 84.7% of patients and 86% reported frequent awakenings with difficulty falling back asleep because of symptoms *(10)*. PLMD increases with age, being uncommon before 30 years of age, seen in 5% of individuals between 30 and 50 years of age, and in about 44% of individuals aged 65 and older *(11)*. One multicenter study found PLMD to be the primary diagnosis in 17% of patients complaining of insomnia *(12)*. Narcolepsy has a prevalence of about 0.05% *(13)*. Fragmented sleep is found in up to 90% of patients with narcolepsy *(14)* and tends to be relatively mild initially, increasing in severity over time *(15)*. Nightmares with a frequency of once a week or greater are seen in 4% of the adult population in Austria *(16)*. One study in France found that 18.3% of insomnia patients were diagnosed as having nightmares *(17)*. Occasional sleep starts are a nearly universal phenomenon. Sleep starts may rarely become repetitive at sleep onset resulting in sleep-onset insomnia.

ETIOLOGY

The cause of insomnia varies according to the primary sleep disorder, and may result from the sleep-onset and maintenance difficulties inherent in the disorder itself or from secondary symptoms of the disorder. For instance, in OSA syndrome, the termination of the apnea is associated with an arousal or awakening that may be perceived and remembered by the patient. OSA syndrome is also associated with other symptoms, such as nocturia and dry mouth, which can contribute to the development of an insomnia complaint. In RLS, the dysesthesias and need to move the legs prevents sleep onset, and may prevent returning to sleep after awakenings in the middle of the night. In PLMD, limb movements are associated with arousals or awakenings that may lead to the perception of difficulty initiating or maintaining sleep. In narcolepsy, the neurochemical defect leads to dysregulation of sleep

architecture, with fragmented nocturnal sleep being a basic manifestation of this dysregulation. Sleep paralysis and hypnogogic hallucinations can be unpleasant enough to result in anxiety about sleeping. The stimulants and antidepressants used to treat excessive daytime sleepiness and cataplexy can further contribute to difficulty sleeping. The anxiety resulting from a nightmare may result in awakenings and difficulty returning to sleep. With sleep starts, an awakening coincides with the abnormal motor activity; when repetitive, this can result in difficulty falling asleep or returning to sleep after awakening in the night.

In the primary sleep disorders, many patients do not develop a complaint of insomnia despite demonstrable sleep fragmentation, suggesting individual differences in susceptibility. Psychophysiological insomnia has been shown to have a familial tendency *(18)*, and genetic predisposition likely plays a role in the development of an insomnia complaint in the primary sleep disorders. Additionally, poor sleep hygiene often develops, leading to further difficulty sleeping. For instance, in RLS, patients often report that they get their best sleep late in the morning, leading to a tendency to sleep in late when possible, leading to further difficulties initiating sleep. In any of the disorders, the perception of difficulty sleeping can lead to anxiety directed toward sleep and therefore a secondary component of psychophysiological insomnia.

PATHOGENESIS AND PATHOPHYSIOLOGY

In OSA, repetitive complete or partial occlusions of the upper airway result in repetitive arousals during sleep. Pharyngeal patency is maintained by a balance of outward forces created by actively contracting pharyngeal muscles such as the genioglossus that are phasically active during inspiration, and negative intraluminal forces created during inspiration *(19)*. In OSA, this patency is compromised through a narrowing of the upper airway through either anatomical means such as hypertrophied tonsils, or dynamic means such as reduction of the phasic inspiratory contractions. This leads to an increased effort of breathing and hypoxemia, resulting in arousals or awakenings, associated with a surge in sympathetic nervous system activity. Because most arousals and awakenings in OSA are brief, patients are usually unaware of the frequency of awakenings. Some awakenings may be long enough for the patient to recall, leading to an insomnia complaint. Apneas are sometimes associated with a sensation of choking, not breathing, dyspnea, or tachycardia. This can lead to a fear of sleep that can sometimes reach phobic levels. The total number of apneic and hypopneic episodes per hour of sleep is called either the apnea-hypopnea index (AHI) or the respiratory disturbance index (RDI), although many laboratories include events such as respiration effort-related arousals or snore arousals in the RDI. An AHI score of 5 or higher is enough to establish the diagnosis of OSA syndrome.

The pathophysiology of RLS remains unclear. Most cases are idiopathic, but a significant percentage are hereditary, with an autosomal-dominant pattern of inher-

itance. A recent study established the presence of a susceptibility locus on chromosome 12q *(20)*. RLS may also be associated with a variety of medical conditions, including neuropathy *(21)*, uremia *(22)*, and iron deficiency *(23)*. Medications such as lithium or antidepressants may precipitate or worsen RLS symptoms *(24–26)*, as may withdrawal from medications such as benzodiazepines or anticonvulsants. Sleep-onset insomnia is induced by the need to move the legs and the accompanying paresthesias. Sleep maintenance difficulties may occur if symptoms are present during nocturnal awakenings. Additionally, most patients with RLS have PLMs while sleeping that may be associated with sleep maintenance difficulties. Although many patients with PLMs during sleep complain of insomnia and daytime sleepiness *(11)*, the relationship between the leg movements and symptoms remains unclear. Mendelson found no correlation between PLM arousal index and subjective complaint of disturbed sleep, subjective measurements of awakening refreshed or Multiple Sleep Latency Test (MSLT) values *(27)*. In a randomized, controlled clinical trial, pramipexole normalized the PLM index in RLS patients without a corresponding improvement in sleep architecture *(28)*.

Although a dysregulation of rapid eye movement (REM) sleep is the most clinically salient feature of narcolepsy, this disorder is also characterized by a dysregulation of other aspects of sleep architecture including sleep continuity. Recent evidence suggests this dysregulation is secondary to a deficiency in hypocretin mechanisms. Narcolepsy in dogs was recently shown to be secondary to mutations in the hypocretin-2 receptor gene *(29)* and hypocretin knockout mice exhibit features characteristic of narcolepsy including episodes of atonia resembling cataplexy and disrupted sleep *(30)*. Most patients with narcolepsy have undetectable cerebrospinal fluid hypocretin *(31)* and histology on six human narcolepsy brains revealed a generalized absence of hypocretin *(31)*. Systemic administration of hypocretin-1 in narcoleptic dogs resulted in improvement in sleep architecture *(33)*.

Nightmares may be triggered by emotionally charged experiences, and when recurrent are felt to reflect unresolved daytime emotional conflicts *(34)*. Nightmares may also be caused by a variety of medications including β-blockers, dopaminergic agents, and some antidepressants *(35–37)*. Nightmares are also a prominent feature of other sleep disorders such as REM sleep behavior disorder. Ethanol withdrawal can cause nightmares so unpleasant that some patients report a resumption of drinking to prevent them *(38)*. The end result is an awakening in which anxiety-arousing dream content is recalled, resulting in prolongation of the awakening. It is unclear if sleep starts are a primary motor disorder or if an abnormality in the sensory system or abnormal central nervous system (CNS) imagery provokes the motor response as a secondary phenomenon.

CLINICAL MANIFESTATIONS

Patients usually have accompanying symptoms that distinguish their sleep disorder and the resulting insomnia from other etiologies of insomnia. Patients with OSA typically have a combination of nocturnal and daytime symptoms that raise

suspicion of the disorder. Nocturnal symptoms include snoring, usually with a crescendo pattern or interruption with snorting or choking noises, witnessed apneas or pauses in snoring, arousals with choking or dyspnea, motor restlessness and limb jerking, night sweats, nocturia, gastroesophageal reflux, and dry mouth and drooling. Daytime symptoms include fatigue, excessive daytime sleepiness, morning headaches, impaired concentration, decreased libido or impotence, and personality changes such as irritability. Although patients present with varying combinations of these symptoms, most of which are very nonspecific, most patients with insomnia secondary to sleep-disordered breathing will give enough symptoms in a careful history to raise suspicion of apnea. Accompanying symptoms may be less prominent in central sleep apnea, but evidence of respiratory failure or underlying CNS or cardiopulmonary disease may be present.

RLS is characterized by four essential features: (1) a desire to move the limbs that is usually associated with dysesthesias or paresthesias, (2) motor restlessness, (3) symptoms that are exclusively present or worsened by rest and relieved at least partially or temporarily by movement, and (4) a circadian rhythm with symptoms that are worse in the evening or night, usually near the patient's habitual bedtime *(39)*. Additionally, most patients have PLMs during sleep and may have involuntary limb movements while awake and at rest. Patients with PLMs without RLS may be unaware of their limb movements. A disheveled bed may provide clues to movements during sleep.

Narcolepsy is characterized by excessive daytime sleepiness accompanied by manifestations of dysregulated REM sleep, including cataplexy, hypnogogic hallucinations, and sleep paralysis *(1)*. Cataplexy is the only symptom that is pathognomonic for narcolepsy but does not occur in all patients. Patients with nightmares are aware of vivid dreaming with anxiety-provoking content. Patients with sleep

Case 1: Narcolepsy Presenting with Insomnia

A 25-year-old man presented with difficulty falling asleep for the past 4 months. Some nights he did not fall asleep until 4 or 5 AM, causing him to be unable to get up in the morning, causing concentration problems during the day, and leading him to frequently fall asleep unintentionally in sedentary situations. The sleepiness affected his life significantly. He had to repeat his second year of medical school because of frequent episodes of falling asleep in class and a lack of concentration.

He did not have a regular bedtime. He reported that some nights he went to bed around 10 PM, some nights 4 AM. Regardless, most nights it took him an hour or more to fall asleep. Even when he got 8 hours of nighttime sleep, he still felt tired in the morning. He was as likely to fall asleep during the day when he got a few hours of sleep as when he got 8 hours of sleep. He did not take naps routinely, but a couple of times per week he fell asleep studying on the couch and usually napped for 1 to 3 hours.

The patient's primary care physician had tried several medications for insomnia including zolpidem, zaleplon, nortriptyline, and trazodone, but nothing helped. The patient's primary care doctor suspected that he was depressed; however, he himself thought that his fatigue and depression were secondary to the insomnia.

The patient denied uncomfortable lower extremity sensations. He denied loud snoring or observed apneas, loss of muscle tone with any particular emotion, sleep paralysis, or hallucinations. He had no past medical history. He was not on any medications on initial presentation and had no family history of insomnia. He did not drink coffee or consume any caffeine in the late afternoon. He did not drink alcohol, did not use illicit drugs, and he quit smoking. His physical exam was normal. His polysomnogram (PSG) was normal and his MSLT showed a mean sleep latency of 3.9 minutes with sleep onset REM periods on three out of five naps.

He was started on modafenil and his nighttime sleep improved and insomnia resolved at a dose of 300 mg taken in the morning. His daytime sleepiness improved significantly at a dose of 600 mg per day.

starts are typically aware of the sudden jerk. They may also experience a sensation of falling, or brief sensory symptoms such as flashes.

DIFFERENTIAL DIAGNOSIS

The symptoms of primary sleep disorders are often nonspecific and the sleep disorders must be differentiated from each other. For instance, periodic limb jerks can occur with PLMD or in OSA syndrome. Sleep paralysis is a prominent manifestation of narcolepsy, but can also occur in any disorder causing sleep fragmentation or severe sleep restriction. It is sometimes difficult to distinguish insomnia secondary to a primary sleep disorder from psychophysiological insomnia. Of 116 patients with sleep-disordered breathing and insomnia in one series, 20 presented with a chief complaint of insomnia only *(5)*. Many patients with insomnia initiated by a primary sleep disorder will develop a component of conditioned insomnia as a secondary phenenomenon. This emphasizes the need for careful evaluation so that symptoms suggestive of a primary sleep disorder are not missed. Patients may develop poor sleep habits such as irregular hours and excessive caffeine intake as an attempt to compensate for symptoms of their sleep disorder, and these features may be so prominent as to suggest that the insomnia is secondary to inadequate sleep hygiene. In primary sleep disorders with longstanding symptoms from an early age, idiopathic insomnia may be the differential diagnosis.

DIAGNOSTIC WORKUP

A thorough history to elicit symptoms of an underlying sleep disorder is essential. Because patients may be unaware of snoring, apneas, and other nocturnal signs,

bedpartners should be interviewed whenever possible. A thorough physical examination should be performed; symptoms elicited during the history may suggest particular systems that require particular emphasis. RLS is a clinical diagnosis based on the four essential clinical features just noted. Polysomnography is not necessary in straightforward cases unless further evaluation for PLMs during sleep is desired. Medical causes should be excluded through careful physical examination and appropriate laboratory evaluation. Nightmares do not require polysomnography unless the history or physical examination leads one to suspect the patient has another contributing sleep disorder. Sleep starts rarely require evaluation beyond a careful history and examination; if features of the history suggest possible seizures, polysomnography with full montage electroencephalogram (EEG) monitoring may be necessary. If OSA or PLMD is suspected, all-night polysomnography is recommended for documentation and determination of severity. If narcolepsy is suspected, then polysomnography followed by MSLT is required for definitive diagnosis. The PSG is a polygraph of EEG findings, eye movements, electromyography readings, oxygen saturation, limb movements, airflow, and chest and abdominal movements taken during sleep, usually for the entire night. An MSLT is a series of four or five opportunities, each separated by a 2-hour interval, to take a 15- to 20-minute nap. The time to the onset of sleep (sleep latency [SL]) is calculated for each nap. The presence or absence of REM sleep is also noted. The mean SL provides a measure of the severity of sleepiness, and the occurrence of REM sleep during the naps is helpful in the diagnosis of narcolepsy. Mean SLs of 5 minutes or less are indicative of pathological sleepiness and SLs of 10 or more are normal. The presence of REM sleep on two or more naps is abnormal and is found in many narcoleptic patients. Nocturnal polysomnography should be performed on the night immediately preceding the MSLT to factor out the impact of sleep deprivation on the mean SL and the patient should be free of any medication effects that may influence sleep.

Case 2: OSA Syndrome Presenting with Insomnia

A 42-year-old man presented with the complaint of approximately a 5-year history of insomnia and severe nighttime snoring. Previously, he was a relatively light, but good sleeper. About 5 years ago he started having problems with sleep maintenance insomnia. He also had snoring at night severe enough for his wife to move out of the bedroom in order to be able to sleep. She also had witnessed some pauses in his breathing. He denied falling asleep in sedentary and unusual situations. He denied falling asleep while at work or driving, but he stated that he feels very fatigued and tired. He denied taking daytime naps. He denied uncomfortable sensations in his legs, morning heartburn, or waking up with a bitter taste in his mouth. He denied morning headaches, morning dry mouth, loss of muscle tone in response to emotions, sleep paralysis, or hypnagogic hallucinations.

His bedtime was between 10 and 11 PM and it took him about 10–15 minutes to fall asleep, however, after 2 or 3 hours he was awake and could not

return to sleep. He tossed and turned for the rest of the night, sleeping only for 30- to 45-minute intervals at a time until his rise time at 6 or 7 AM. Although he felt restored most of the time, he also had significant fatigue during the day.

He had no allergies, was not presently on any medications except vitamins, and did not have a past medical history. There was a family history of snoring and insomnia in one parent and one sibling. He consumed large amounts of caffeine but did not smoke and used alcohol only in social settings. A review of systems was significant for a 25-lb weight gain over the past year. His physical exam was normal.

The patient underwent a PSG that revealed reduced sleep efficiency and an RDI of 49.9 breathing events per hour. The lowest oxyhemoglobin saturation was 70%. Following the diagnostic portion of the study, a nasal continuous positive airway pressure (CPAP) trial was initiated. A pressure of 7 cm H_2O was found to be optimal.

The patient's symptoms resolved completely after initiation of CPAP. At the 3-month follow-up visit, he reported consolidated sleep at night and no more daytime fatigue as well as resolution of snoring.

PREVENTION

Not enough is known about the etiology of narcolepsy, RLS, PLMD, or sleep starts to allow effective prevention. OSA syndrome is amenable to some preventive measures, such as maintenance of lean body weight, avoidance of ethanol and other CNS depressants near bedtime, and avoidance of smoking. Many patients, however, will develop OSA even when known risk factors are not present. Although there is little objective data on prevention of sleep disturbance from nightmares, teaching patients effective methods to deal with emotional stresses and trauma may help minimize sleep disturbance from nightmares. In all patients, teaching good sleep hygiene and treating secondary conditioned insomnia may minimize insomnia symptoms resulting from the primary sleep disorder.

Case 3: RLS Presenting with Insomnia

A 50-year-old woman presented for a 4- to 5-year history of inability to fall asleep. Over the past 4–5 years, she experienced significant trouble falling asleep, mainly due to uncomfortable, indescribable feelings in her legs and sometimes in her arms when she was trying to fall asleep. This discomfort was usually relieved by moving or rubbing her feet. Occasionally, it woke her up from sleep as well. She experienced this about two to three times a week. She also complained of the same discomfort, although less frequently, during the day when sedentary. For example, when she was sitting at her desk at work or when she was riding in a car or an airplane, she often had to get up

and walk to relieve these symptoms. She was initially treated with amytriptiline with only worsening of her symptoms and no relief.

She was tired during the day, but did not fall asleep inappropriately. Her husband denied she had any kind of leg movements in her sleep. He denied that she snored or gasped for air or that she had any pauses in her breathing while asleep.

In the past, before this last 5 years, she had experienced these symptoms periodically about five times in her life, mainly in the last trimester of each of her pregnancies.

Her past medical history included hypertension, hysterectomy, carpal tunnel surgery, window placement in her sinuses, and appendectomy. She was presently taking Maxzide and reported an allergy to codeine.

She did not smoke or drink alcohol. She did not abuse drugs. Her family history was significant for RLS in her mother. This was never formally diagnosed, however. Her physical exam was normal.

The patient was diagnosed with RLS and started on 0.125 mg of pramipexol at bedtime and an additional 0.125 mg dose as needed during the day. Her symptoms completely resolved on this regimen.

PROGNOSIS AND COMPLICATIONS

The prognosis is good if the underlying sleep disorder can be effectively treated and secondary causes of insomnia such as poor sleep hygiene and conditioned insomnia can be addressed. If the underlying sleep disorder is not effectively treated or the perpetuating factors are not recognized and treated, then insomnia can persist or worsen. Complications include hypnotic dependence, ethanol abuse, and persistent insomnia is a risk factor for depression *(40,41)*.

MANAGEMENT

Effective management requires that the underlying sleep disorder be appropriately diagnosed and treated. For OSA, general recommendations such as weight loss if obesity is present and avoidance of CNS depressants at bedtime are made to all patients. In some patients, apnea may be significant only in the supine position; in these patients an irritating object such as a tennis ball in a stocking affixed to the back of a nightgown to promote sleep in the lateral position may be sufficient therapy. Nasal CPAP remains the gold standard treatment and breathing may be normalized in most patients, although compliance can be problematic. Patients with a significant insomnia complaint may find CPAP uncomfortable and it may be difficult to obtain compliance with therapy. In these patients, time-intensive desensitization techniques may be helpful. In carefully selected patients, hypnotic administration to promote CPAP compliance may be appropriate. Surgery on the upper airway and therapy with an oral prosthesis are other alternative treatments.

Treatment of RLS should begin with treating any precipitating or aggravating conditions such as iron deficiency anemia, and the elimination of aggravating medications if possible. Caffeine and other methylxanthines may aggravate symptoms and reduction or elimination of these should be attempted. Nonpharmacological treatments such as massage and stretching or hot baths are beneficial for some patients. Effective pharmacological therapies include dopamine agonists such as ropinerole or pramipexole, benzodiazepines, or opiates. Several anticonvulsants, most notably neurontin, have been reported to be beneficial. Most patients obtain at least partial relief of their symptoms. PLMs are treated by the same pharmacological agents as RLS. Although reduction in leg movements can usually be achieved, symptom reduction is less reliable *(42)*.

Treatment of the sleep disturbance in narcolepsy can be problematic as agents used to promote daytime alertness can aggravate insomnia, and medications used to promote sleep can worsen daytime sleepiness. Treatment options include the use of a short-acting benzodiazepine agonist or a sedating tricyclic antidepressant. Xyrem was recently approved to treat cataplexy in narcolepsy patients. Xyrem has hypnotic properties and improves daytime alertness, making it a promising medication for many narcolepsy patients with insomnia *(43)*.

Treatment modalities for nightmares include psychotherapy, systematic desensitization and relaxation techniques, imagery rehersal, eye movement desensitization, and hypnosis *(44–48)*. Hypnotic medications benefit patients with repetitive sleep starts.

All patients with insomnia secondary to these sleep disorders may develop perpetuating factors such as poor sleep hygiene and conditioned insomnia and may require training in sleep hygiene and behavioral therapy for the conditioned insomnia. Judicious use of hypnotic medications may be indicated, although the clinician should remain aware of the potential for some medications to worsen OSA syndrome.

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IV Treatment of Insomnia

13

Cognitive-Behavioral Therapy for Insomnia

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INTRODUCTION

This chapter provides an overview of how primary insomnia is assessed and treated using cognitive-behavioral therapy (CBT). Additionally, we provide some upfront information that reviews the CBTs regarding the etiology of chronic insomnia and some follow-up information of the efficacy of CBT for insomnia. The former is provided so that the reader may appreciate the principles on which CBT is founded. The latter is provided so that the reader may appreciate the extent to which CBT for insomnia has been empirically validated.

THEORETICAL PERPSECTIVES ON INSOMNIA

Behavioral Perspective

Since the late 1980s, insomnia has largely been conceptualized from within a behavioral framework. The original model was proposed by Spielman and colleagues and it continues to be the leading theory for both sleep medicine and the subspecialty area of behavioral sleep medicine *(1)*. As illustrated in Fig. 1, the behavioral model posits that insomnia occurs acutely in relation to both predisposing (trait) and precipitating (state) factors and occurs chronically in relation to perpetuating or maintaining factors. Thus, an individual may be prone to insomnia due to trait characteristics, experience acute episodes because of precipitating events, and have chronic insomnia owing to a variety of perpetuating factors.

With respect to trait factors, personality characteristics *(2,3)*, physiological arousal *(2,3)*, and genetic predisposition *(4)* are each thought to contribute to predispose the individual to acute episodes of insomnia. Typical precipitating events (which represent stressors within the larger stress diathesis model of disease) include situational stress *(5)*, acute injury or pain, bereavement, and so on. Perpetuating factors, as the term implies, maintain the chronic form of the disorder even

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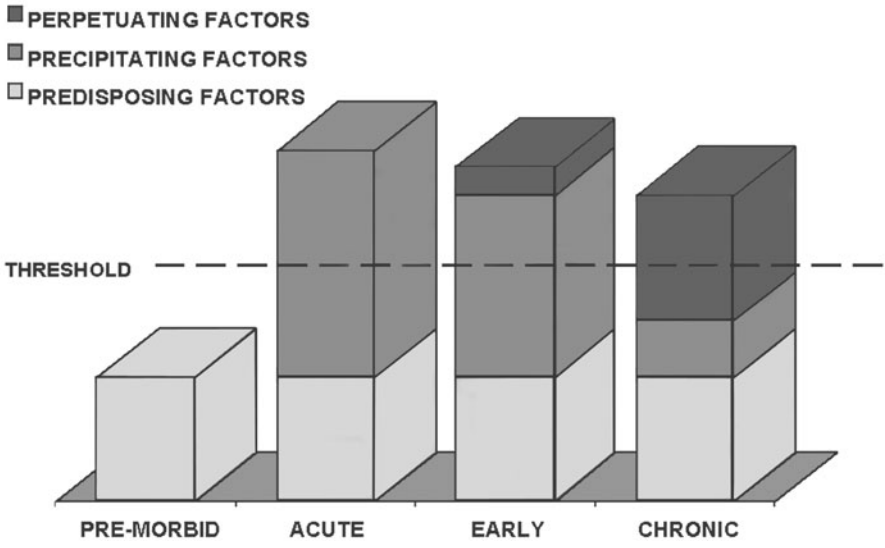

Fig. 1. A schematic of the differential diagnosis process for the diagnosis of primary insomnia.

after the precipitating events have either been stabilized or resolved. Perpetuating factors are any of a variety of compensatory strategies in which the patient engages in an attempt to cope with insomnia symptoms. Typical examples of such factors include excessive daytime napping, extending sleep opportunity, keeping variable sleep–wake schedules, use of alcohol as a hypnotic, spending excessive time awake in bed, diminishing daily activity level due to fatigue, and so on.

Central to the behavioral model of chronic insomnia is the role of classical conditioning as the primary maintaining factor. It is hypothesized that, over time, insomnia becomes a conditioned response to the bed and bedroom environment. This process presumably occurs via traditional principles of classical conditioning, resulting from repeated pairings of the bed and bedroom (conditioned stimuli) with states of psychophysiologic hyperarousal (unconditioned stimuli) that are thought to interfere with the normal biological processes of sleep initiation and maintenance.

Cognitive Perspective

A number of authors have stressed the importance of cognitive factors in primary insomnia *(6–8)*. Given their emphasis on the role of cognition, they and others have developed interventions, which provide for the cognitive component of the more broad-based cognitive-behavioral approach. Within this perspective, two related types of cognitions are thought to be operational: one set is related to the patient's beliefs about his or her disorder; the other is related to cognitive processes like intrusive thoughts and worry.

Morin et al., for example, found that patients with primary insomnia have a number of maladaptive beliefs about sleep, including unrealistic views about what constitutes adequate sleep and catastrophic beliefs about the consequences of insomnia. Such beliefs presumably contribute to insomnia by increasing sleep-related performance anxiety and by prompting and promoting maladaptive compensatory behaviors. Support for the role of such factors derives from data showing that successful CBT of insomnia is associated with a reduction in negative beliefs and attitudes about sleep *(9,10)*. Although this is suggestive, more work is needed to demonstrate the "insomnogenic" potential of such cognitions. This is so because one can easily imagine that successful therapy may change one's thoughts and beliefs, but also that such changes may not be responsible for the treatment gains.

Hall et al. and Harvey and colleagues focused more on cognitive process (vs content) issues (*5,8)*. Central to this area is that patients with insomnia often complain that they are unable to sleep because of intrusive thoughts or excessive worry. These thoughts and images are characterized as being "intrusive" and may occur in isolation or as unwanted perseverative-type problem solving (worry). The content of the "thoughts and worry" may be centered on the kind of dysfunctional attitudes and beliefs described previously, but they are often more general in content. The ideation and imagery that occurs as intrusive thoughts is often related to mundane daily activities and/or work or relationship issues. As with dysfunctional attitudes and beliefs, intrusive thoughts and perseverative thinking (from within the radical cognitive perspective) are thought to be responsible for the occurrence and severity of insomnia. The more moderate view is that these phenomena are, along with behavioral and conditioning factors, contributory.

Support for the cognitive perspective comes from a variety of studies that have found that patients with primary insomnia complain of higher levels of pre-sleep rumination compared to normal controls *(11,12)*. Investigations of pre-sleep thought content have found that the pre-sleep cognitions of patients with primary insomnia tend to be more negatively toned, and that patients report increased general problem solving and thoughts pertaining to environmental stimuli at or around sleep onset *(13–15)*.

Neurocognitive Perspective

In sharp contrast to the cognitive model, the neurocognitive perspective all but suggests that dysfunctional beliefs and worry are epiphenomena. It is posited that cognitive factors are likely to mediate the occurrence and severity of insomnia when the disorder is acute. When, however, the disorder is chronic, cognition occurs secondary to conditioned arousal. Put differently, patients with chronic insomnia are not awake because they are given to rumination and worry, but rather ruminate because they are awake.

The neurocognitive perspective *(3)* is an extension of the traditional behavioral model. As laid out by Spielman and colleagues *(1)*, the behavioral model allows for a compelling conceptualization regarding how maladaptive behaviors lead to con-

ditioned arousal and chronic insomnia. The Spielman model does not, however, spell out what the conditioned arousal is, or why and how "arousal" interferes with sleep initiation and/or maintenance and/or the perception of sleep. These latter issues are precisely the province of the neurocognitive model that defines "arousal" as conditioned cortical arousal. This form of arousal may be observed in patients with primary insomnia as high frequency electroencephalogram (EEG) activity (14–45 Hz) at or around sleep onset and during non-rapid eye movement (NREM) sleep *(15,16)*. High-frequency EEG activity, it is hypothesized, allows for abnormal levels of sensory and information processing and long-term memory formation. Increased sensory processing is thought to interfere with the ability to initiate sleep (as measured by traditional polysomnographic measures). Increased information processing during polysomnographic-defined sleep is thought to interfere with the subject's ability to perceive polysomnographic sleep as "sleep." Increased long-term memory formation (attenuation of the normal mesograde amnesia of sleep) is thought to interfere with the patient's morning judgments about sleep quality and quantity.

Support for the neurocognitive perspective *(17)* comes from a variety of studies that have found β EEG (14–45 Hz) (1) to be elevated in patients with insomnia *(16,18–21)*, (2) to be positively associated with patient perceptions of sleep quality *(22,23)*, (3) to be positively associated with sleep state misperception (SSM; the degree of discrepancy between subjective and objective measures of sleep) *(16,24)*, and (4) to vary with successful CBT treatment for insomnia *(25)*. There is also preliminary evidence that the occurrence of elevated NREM β activity is sensitive and specific to primary insomnia (vs insomnia secondary to major depressive disorder) *(16)* and data that suggest the long-term memory function at peri-sleep onset intervals is altered in patients with chronic insomnia *(26)*.

ASSESSMENT AND MEASUREMENT

Self-Report Assessment

Behavioral sleep medicine specialists often utilize a number of retrospective assessment tools to gather more precise diagnostic information. Additionally, behavioral sleep medicine specialists utilize daily sleep diaries *(27)* to prospectively monitor sleep complaints. Prospective assessment is important for evaluating the severity of insomnia complaints on a day-to-day basis, identifying the behaviors that maintain the insomnia, determining the extent to which circadian dysrhythmia is present, and gathering the data needed to measure and guide treatment response.

The sleep component of sleep–wake diaries are typically completed after waking and obtain information on time to bed, wake time, sleep latency (SL), frequency of nightly awakenings (FNA), wake time after sleep onset (WASO), total sleep time (TST), early morning awakenings (EMA), medication/ substances taken before bed, and subjective assessments of sleep quality. The daytime measures, which are completed prior to going to bed, include nap frequency and duration, fatigue ratings, stimulant consumption, and medication usage.

Objective Assessment

In current clinical practice, the diagnosis of primary insomnia does not require an in-laboratory, polysomnographic study to substantiate the diagnosis. This is true for three reasons. First, there is enough of a general correspondence between the subjective complaint and objective measures so that polysomnographic assessment is not required to verify the sleep continuity disturbance. Second, traditional polysomnography does not reveal, or allow for the quantification of, the underlying sleep pathophysiologies that presumably give rise to the patient's complaints. Third, and most pragmatically, third-party payers will not reimburse for sleep studies on patients with likely primary insomnia. However, sleep studies are indicated if the patient demonstrates symptoms consistent with other intrinsic sleep disorders and/or fails to respond to treatment.

When assessed with polysomnography, patients with primary insomnia reliably exhibit increased SL, increased FNAs, increased WASO time, and decreased TST relative to good sleeper controls. Polysomnographic findings, however, do not correspond in a one-to-one fashion to patient perceptions of sleep continuity. Patients with insomnia routinely report more severe sleep disturbance than is evident on traditional polysomnographic measures *(28–30)*. Some have argued that this discrepancy might be explained by the findings that patients with primary insomnia show a greater degree of psychopathology, including tendencies to somatize internal conflicts and exaggerate symptoms *(31–33)*. Others have argued that the subjective–objective discrepancy findings reflect a cardinal feature of the disorder, that is, the persistence of sensory and information processing into NREM sleep. The continuance of such processes into polysomnographic-defined sleep are thought to be the basis for patient difficulties distinguishing between wakefulness and sleep (3). The extent to which one or both of these factors contributes to the discrepancies between subjective and objective measures of sleep in insomnia continues to be a matter of ongoing debate. (For additional information on these issues, please see the following section on the cognitive-behavioral perspective on insomnia.)

When polysomnography is not feasible, the use of alternative, less costly objective devices can be particularly helpful when the clinician suspects a high degree of SSM. SSM is a term (as well as disorder) used to describe the common finding among patients with insomnia that there is a discrepancy between a patient's subjective impression of sleep parameters and what is measured via objective recording methods. At the level of self-report, extreme values (gathered retrospectively or prospectively) may suggest that this is a component of the disorder (e.g., SLs >2 hours, WASO >2 hours, or a TST of ≤4 hours). In the absence of a polysomnographic study, actigraphs may be used to obtain corroborating prospective data. Actigraphs are wristwatch-like devices that utilize sophisticated movement detectors to estimate the traditional sleep continuity parameters (e.g., SL, WASO, FNA, and TST). This information may, in turn, be compared to the self-report data to assess the degree to which SSM is occurring. The extent to which subjective–objective discrepancies can be resolved using actigraphy has not been

subjected to empirical validation. In our clinical practice, however, we have found that actigraphy can be used to assess for SSM.

COGNITIVE-BEHAVIORAL TREATMENT

The most common CBTs for primary insomnia are sleep hygiene education, stimulus control therapy (SCT), sleep restriction therapy (SRT), relaxation training, and cognitive therapy. (For a detailed explanation of each of these therapies *see* ref. *6*.)

Of all the available psychological treatments, SCT is the most well-validated and is considered the "gold standard" for the behavioral treatment of insomnia. In practice, most behavioral sleep medicine clinicians adopt a multicomponent approach that usually contains SCT, SRT, and sleep hygiene therapy.

Therapeutic Regimen

The CBT of insomnia generally requires 4 to 8 weeks time with once-a-week, face-to-face meetings with the clinical provider. Sessions range from 30 to 90 minutes depending on the stage of treatment and the degree of patient compliance. Intake sessions are usually 60 to 90 minutes in duration. During this session, the clinical history is obtained and the patient is instructed in the use of sleep diaries. No intervention is provided during the first week. This time frame is used to collect the baseline sleep–wake data that will guide treatment for the balance of therapy. The primary interventions (SCT and SRT) are deployed over the course of the next one to two 60-minute sessions. Once these treatments are delivered, the patient enters into a phase of treatment where TST is upwardly titrated over the course of the next two to five visits. These follow-up sessions require about 30 minutes, unless additional interventions are being integrated into the treatment program or extra effort is required to gain patient compliance. Adjunctive treatments include cognitive therapy, relaxation training, and relapse prevention.

First-Line Interventions

Stimulus Control Therapy

SCT is recommended for both sleep initiation and sleep maintenance problems. SCT is generally considered the first-line behavioral treatment for chronic primary insomnia because it has the most research support *(34)*. SCT instructions limit the amount of time patients spend awake in the bed/bedroom, and are designed to decondition pre-sleep arousal and re-associate the bed/bedroom environment with rapid, well-consolidated sleep. Typical instructions include (1) maintaining a fixed wake time 7 days a week, irrespective of how much sleep one gets during the night; (2) avoiding any behavior in the bed or bedroom other than sleep or sexual activity; (3) sleeping only in the bedroom; (4) leaving the bedroom when awake for approximately 15 to 20 minutes; (5) returning to the bedroom only when sleepy. Some clinicians, in an effort to prevent "clock-watching" behavior, encourage patients to leave the bedroom as soon as they feel "clearly awake" or experience annoyance

and irritation over the fact that they are awake. The combination of these instructions re-establishes the bed and bedroom as strong cues for sleep, and entrains the circadian sleep–wake cycle to the desired phase.

Sleep Restriction

SRT is recommended for both sleep initiation and sleep maintenance problems. SRT requires patients to limit the amount of time in bed (TIB) to an amount equal to their average TST. In order to accomplish this, the clinician works with the patient to establish a fixed wake time and decrease sleep opportunity by limiting the subject's TIB to an amount that equals his or her average TST as ascertained by baseline sleep diary measures. Once a target amount of TIB is set, the patient's bedtime is delayed to later in the night so that the TIB and average TST are the same. Initially, this intervention results in a reduction in TST, such that the patient gets less total sleep than he or she is accustomed to. This controlled form of sleep loss usually corresponds to a decrease in SL and WASO time. Thus, during the acute phase of treatment, the patient gets less sleep, but sleeps in a more consolidated fashion (i.e., he or she fall asleeps more quickly and stays asleep for longer periods of time). The increase in consolidated sleep is formally represented as sleep efficiency (TST/TIB).

The patient's sleep efficiency is monitored on a weekly basis. If the patient's average weekly sleep efficiency reaches 85–90% (depending on age), then sleep opportunity is incrementally increased by 15 minutes. The increase in sleep opportunity is accomplished by having the patient retire 15 minutes earlier for the next week of treatment. The upward titration process is usually continued for about 4 weeks, thus allowing for an increase of about 1 hour in sleep opportunity. When the patient does not reach the 85–90% benchmark, some clinicians reduce the total sleep opportunity to the previous "set point," others maintain the subject's total sleep opportunity until adequate sleep efficiency is observed, whereas still others combine these approaches. With respect to the last possibility, the clinician may maintain the subject's total sleep opportunity for 2–3 weeks and then downwardly titrate the TIB when there is clear evidence that the patient cannot sustain his or her clinical gains.

SRT is thought to be effective for two reasons. First, it prevents the patient from coping with his or her insomnia by extending sleep opportunity. This strategy, although increasing the opportunity to get more sleep, produces a form of sleep that is shallow and fragmented. Second, the initial sleep loss that occurs with SRT is thought to increase the "pressure for sleep," which in turn produces quicker SLs, less WASO, and more efficient sleep.

Three points merit further comment. First, total TIB is manipulated by phase delaying the patient's sleep period. This, along with keeping a fixed wake time, results in sleep restriction. It is plausible, however, that total TIB could be altered by having the subject wake up at an earlier time. This approach is not adopted because fixing "wake up time" at an early hour (1) does not capitalize on the fact that extending wakefulness is easier to tolerate than curtailing sleep, (2) delays the initial increase in time awake before sleep for 24 hours (and thus delays the clinical

effect), (3) may reinforce the tendency for EMAs, and (4) undermines the opportunity to pair "sleep" with the bed/bedroom.

Second, it should be noted that SRT has some paradoxical aspects. One paradox is that patients who report being unable to sleep are in essence being told to sleep less. The other paradox occurs over the course of treatment. With therapy, patients find that it is difficult to stay awake until the prescribed hour. This, if not paradoxical, is at least ironic for the patient who initially presents with sleep-onset difficulties. Finally, it should be noted that SRT may be contraindicated in patients with histories of mania or seizure disorder because it may aggravate these conditions.

Adjunctive Interventions

Sleep Hygiene Education

Sleep hygiene education is recommended, along with SRT and SCT, for both sleep initiation and maintenance problems. It may also have some value as a means toward increasing TST. Sleep hygiene education addresses a variety of behaviors that may influence sleep quality and quantity. The intervention most often involves providing the patient with a handout and then reviewing the items and the rationales for them. Table 1 contains a set of sleep hygiene instructions. It should be noted that in this formulation, several aspects of other therapies are adopted. For example, items 1, 2, 12, 13, and 15 are traditionally considered part of SCT and/or SRT.

Sleep hygiene education is most helpful when tailored to a behavioral analysis of the patient's sleep–wake behaviors. The tailoring process allows the clinician the opportunity to (1) demonstrate the extent to which he or she comprehends the patient's individual circumstances (by knowing which items do and do not apply), (2) suggest modifications, and (3) show the patient the rules, which are in many ways too "absolutistic." Consider the following two examples:

- The admonishment to avoid caffeinated products may be, in general, too simply construed. Caffeinated beverages may be used to combat daytime fatigue (especially during acute therapy) and, if the withdrawal is timed correctly, may actually enhance the subject's ability to fall asleep.
- The prohibition against napping may not be practical. Elderly subjects or subjects with extreme work performance demands may indeed need to compensate for sleep loss. A more considerate approach to napping may entail taking into account the time of the nap, the duration of the nap, and how nocturnal sleep is handled on days when subjects nap. Napping earlier in the day will allow for more homeostatic pressure for nocturnal sleep. Limiting the duration of the nap will allow for less of a discharge of the homeostat and enhance the subjects sensation of feeling rested from the nap (by avoiding awakening from slow wave sleep). Going to bed later, when one naps during the day, may minimize the effects of the nap on nocturnal sleep.

Finally, it can be argued that the most important aspect of sleep hygiene education derives not so much from the "tips" provided, but from allowing the clinician the opportunity to demonstrate his or her knowledge. A thoughtful and elaborate review may enhance the patient's confidence in the therapist and in the treatment regimen. Such enhanced confidence may lead to greater adherence or compliance with the more difficult aspects of therapy.

Table 1
Sleep Hygiene Instructions

1. Sleep only as much as you need to feel refreshed during the following day. Restricting your time in bed helps to consolidate and deepen your sleep. Excessively long times in bed lead to fragmented and shallow sleep. Get up at your regular time the next day, no matter how little you slept.
2. Get up at the same time each day, 7 days a week. A regular wake time in the morning leads to regular times of sleep onset, and helps to set your "biological clock."
3. Exercise regularly. Schedule exercise times so that they do not occur within 3 hours of when you intend to go to bed. Exercise makes it easier to initiate sleep and deepen sleep.
4. Make sure your bedroom is comfortable and free from light and noise. A comfortable, noise-free sleep environment will reduce the likelihood that you will wake up during the night. Noise that does not awaken you may also disturb the quality of your sleep. Carpeting, insulated curtains, and closing the door may help.
5. Make sure that your bedroom is at a comfortable temperature during the night. Excessively warm or cold sleep environments may disturb sleep.
6. Eat regular meals and do not go to bed hungry. Hunger may disturb sleep. A light snack at bedtime (especially carbohydrates) may help sleep, but avoid greasy or "heavy" foods.
7. Avoid excessive liquids in the evening. Reducing liquid intake will minimize the need for nighttime trips to the bathroom.
8. Cut down on all caffeine products. Caffeinated beverages and foods (coffee, tea, cola, chocolate) can cause difficulty falling asleep, awakenings during the night, and shallow sleep. Even caffeine early in the day can disrupt nighttime sleep.
9. Avoid alcohol, especially in the evening. Although alcohol helps tense people fall asleep more easily, it causes awakenings later in the night.
10. Smoking may disturb sleep. Nicotine is a stimulant. Try not to smoke during the night when you have trouble sleeping.
11. Don't take your problems to bed. Plan some time earlier in the evening for working on your problems or planning the next day's activities. Worrying may interfere with initiating sleep and produce shallow sleep.
12. Train yourself to use the bedroom only for sleeping and sexual activity. This will help condition your brain to see bed as the place for sleeping. Do *not* read, watch TV, or eat in bed.
13. Do not *try* to fall asleep. This only makes the problem worse. Instead, turn on the light, leave the bedroom, and do something different like reading a book. Don't engage in stimulating activity. Return to bed only when you are sleepy.
14. Put the clock under the bed or turn it so that you can't see it. Clock watching may lead to frustration, anger, and worry, which interfere with sleep.
15. Avoid naps. Staying awake during the day helps you to fall asleep at night.

Note. The list includes the usual practices described as "good sleep hygiene," but it also includes some principles subsumed under stimulus control therapy (principles 2,12,13), sleep restriction therapy (principles 1,2,15), and relaxation (principles 11,13).

Cognitive Therapy

Several forms of cognitive therapy for insomnia have been developed. Some have a didactic focus *(6)*, some use paradoxical intention *(35)*, others employ "distraction and imagery" *(36)*, and still others use a form of cognitive restructuring *(37)*. Although the approaches differ in procedure, all are based on the observation that patients with insomnia have negative thoughts and beliefs about their condition and its consequences. Helping patients challenge the veracity of these beliefs is thought to decrease the anxiety and arousal associated with insomnia. The cognitive restructuring approach, adapted from for the procedure used for panic disorder *(38-40)*, is illustrated below.

Cognitive restructuring focuses on catastrophic thinking and the belief that poor sleep is likely to have devastating consequences. Although psychoeducation may also address these kinds of issues, the more important ingredient of cognitive restructuring lies not in disabusing the patient of erroneous information, but rather in having the patient discover that his or her estimates are ridiculously inaccurate (a testament to the tendency to think in less than clear terms in the middle of the night). When undertaking this exercise with a patient, it needs to be introduced in a considerate way, one that avoids any hint that the therapist is being pedantic, patronizing, or condescending.

The following are examples of the catastrophic thinking that occurs when the patient is lying in bed trying to sleep...

"If I don't get a good night's sleep,

I'll be in a bad mood tomorrow. If my mood is poor tomorrow, I will—yet again—be short with my wife. If I'm irritable with my wife (again), she may start thinking about not putting up with this anymore. If she thinks about not putting up with this anymore, she'll consider leaving me..." [get divorced].

I won't be able to stay awake or concentrate when I'm driving to work. If I don't stay awake or concentrate when I'm driving, I may get into an accident..." [wreck the car].

I won't be able to function tomorrow at work. If I am not able to function at work, I may get a reprimand. If I get reprimanded... " [get fired].

The first step in the cognitive restructuring process is to have patients discuss and list the kinds of negative things they think can happen when their sleep is poor. Usually, the list is constructed with the patient and placed, as a chart, on the cognitive therapist's ever present in-office chalkboard. The first column in the chart lists catastrophic events. Note that the patient may need to be prompted to identify the underlying and most catastrophic thought. For example, the patient may say "I worry about not being able to fall sleep" when what he or she is primarily worried about is the extreme version of this proposition: spending the entire night awake.

Once the list is compiled (5 to 10 things constitutes a reasonable list), patients are then asked how likely they think each of the events are, given a night of poor

sleep. For instance, the therapist may ask, "When you are lying in bed imagining being so tired tomorrow that you might perform badly at work, at that moment how certain are you that your work will be 'substandard', how certain are you that you'll be 'reprimanded,'" and so on. These data are represented in column 2. Next, the patient is asked how frequently his or her sleep is poor, and for how many years he or she has been suffering from insomnia. This number is coded as the "number of days with insomnia" and is set to the side of the table (to be coded later in column 3). The final data needed from the patient is an estimate of how frequently each of the catastrophic events have occurred. These are coded into column 4. The combination of these four sources of data are then used to show the patient that there is a substantial mismatch between his or her degree of certainty and the number of times the negative events have actually transpired.

For example, the clinician might observe, "You have suffered from insomnia for 5 nights a week for the last 3 years. This means that you have had about 800 really bad nights. You also said that when you're thinking about what might happen if you don't fall asleep, you are 90% certain that on the next day you are going to perform so badly that you'll be reprimanded. If it happened 90% of the time and you've had 800 bad nights, then you should have been reprimanded about 700—lets say 500—times." These data are represented in column 5. The last column of data is then compared to the list in column 4, so that the patient can see the mismatch between the number of instances that should have occurred and the number of instances that actually occurred. For an example of the chart just described, *see* Table 2.

Relaxation Training

Different relaxation techniques target different physiological systems. Progressive muscle relaxation is used to diminish skeletal muscle tension *(41–45)*. Diaphragmatic breathing is used to make respiration slower, deeper, and mechanically driven from the abdomen as opposed to the thorax. (It is interesting to note that this form of respiration resembles what occurs naturally at sleep onset.) Autogenic training focuses on increasing peripheral blood flow by having subjects imagine, in a systematic way, that each of their extremities feel warm.

Most practitioners select the optimal relaxation method based on which technique is easiest for the patient to learn and which is most consistent with how the patient manifests arousal. Like cognitive techniques, learning to effectively use relaxation training often requires substantial practice. Many clinicians recommend the patient rehearse the skill during the day in addition to practicing prior to sleep. If relaxation training causes some initial "performance anxiety" when integrating it into SCT instructions, it may be best to have the patient practice in a room other than the bedroom. It also should be kept in mind that some patients, especially those with a history of panic disorder, may experience a paradoxical response to relaxation techniques.

Phototherapy

Although many clinicians may not consider phototherapy a behavioral intervention, it is often important to integrate the use of bright light into the treatment regi-

Table 2
Cognitive Restructuring

1	2	3	4	5
Catastrophic events	Certainty when lying awake and unable to sleep	No. days with insomnia	No. of event occurrences	No. of event occurences given certainty
Get reprimanded Get fired Get divorced Wreck the car Be awake all night	90%	800	5	620 (500)

men. This is especially true when circadian factors appear to substantially contribute to the insomnia complaint. There is substantial empirical evidence that bright light has sleep-promoting effects.

In the case where the patient's insomnia has a phase-delay component (i.e., the patient prefers to go to bed late and wake up late), bright light exposure in the morning for a period of 30 minutes or more may enable the patient to "feel sleepy" at an earlier time in the evening. In the case where the patient's insomnia has a phase-advance component (i.e., the patient prefers to go to bed early and wake up early), bright light exposure in the late evening/early night may enable him or her to stay awake until a later hour. Phototherapy is often accomplished via a light box that typically generates white light, or more selectively, blue spectrum light at 5000–10,000 lux. The dose is adjusted by altering the distance and duration of light exposure. It is generally assumed that phototherapy has no significant side effects, but this is not always the case. Mania may be triggered by bright light, but rarely, if ever, in patients not previously diagnosed with bipolar mood disorder. Other side effects are insomnia, hypomania, agitation, visual blurring, eye strain, and headaches. Light boxes may not be recommended for individuals with certain eye conditions, including retinopathy secondary to diabetes. In some cases, equivalent or better phase-shifting properties may be accomplished by scheduling time outdoors (e.g., taking early morning walks).

The sleep-promoting effects of bright light may occur via several mechanisms, including shifting the circadian system, enhancement of the amplitude of the circadian pacemaker, promoting wakefulness during the day and sleep at night, or indirectly, via its antidepressant effects.

Complicating Factors

There are a number of potential complicating factors that require continuous monitoring and evaluation throughout the course of treatment, particularly if the patient fails to show expected clinical gains after two to four sessions of active treatment. The most common complicating factors are poor treatment compliance,

issues related to comorbid psychiatric and medical disorders, and the simultaneous use of sedative hypnotics.

Treatment Compliance

The single most important complicating factor is poor treatment compliance. At the beginning of treatment, the clinician should proactively address the fact that the prescriptions may seem counterintuitive and that adhering to the treatment will be difficult. Providing the patient with a complete and thoughtful rationale for each aspect of the treatment, managing the patient's expectations, and encouraging an active self-management approach are essential. Providing the rationale for treatment is likely to gain patient compliance in at least two ways. First, the effort to explain therapy is less imperative, thereby making the patient an active partner in the treatment process and making him or her less resistant or reactive to the prescriptions. Second, a fluid, interesting, and compelling explanation will support and enhance the patient's perception of the clinician as a competent authority.

With respect to expectation, the patient should not anticipate that the results will be immediate. In fact, the patient should be cautioned that his or her sleep problem is likely to briefly "get worse before it gets better." Sometimes an appeal to the research literature, demonstrating that treatment gains are maintained and often continue to improve in the long-term, may help maintain the patient's motivation despite the short-term difficulty adjusting to the procedures.

With respect to "active self-management," it is important to remember that the treatment alternative is medication and that this requires very little in the way of lifestyle change. Thus, the clinician must spend a considerable amount of time working with the patient to "make and stay with the investment."

Comorbity of Mental and Medical Disorders

Many patients with chronic insomnia report mild or subthreshold levels of depressive symptoms. When depressive symptoms become severe, they may interfere with the patient's ability and motivation to successfully follow the recommended protocol. If medical factors become exacerbated, expectations for clinical gains need to be tempered until stabilization occurs. Throughout the course of treatment, both medical and psychiatric factors should be monitored and consideration should be given for further evaluation and intervention.

CBT and Sedative Hypnotics

Not yet addressed is the possibility of using sedative hypnotics acutely, along with CBT for insomnia (i.e., dual or combined therapy). This is a promising and underinvestigated area of inquiry. Initial studies were mixed *(46–48)*, but promising work continues *(49)*. The benefit of combined therapy is a more rapid reduction of symptoms. The risk of combining pharmacotherapy with behavioral treatment, however, is that once patients start using medications, they may be less inclined to adopt or tolerate behavioral interventions. Work is ongoing to determine the most effective way to combine these two strategies to capitalize on the immediate reduction in symptoms afforded by sedative hypnotics and the long-term efficacy of CBT *(50)*.

Perhaps more important than the issue of combined therapy to the practice of CBT for insomnia is that many of the patients referred for CBT have been taking sedative hypnotics for years and are very apprehensive about discontinuing treatment. Often, the initial phases of treatment involve collaboration with the referring physician to assist the patient in the weaning process. Use of sleep diaries to provide feedback about sleep continuity during the withdrawal process and education about rebound insomnia and the medication itself are important for this kind of intervention. It should be noted that the chronic use of sedative hypnotics often leaves the patient with as poor a sleep continuity profile as if no medications at all were being used. This is difficult for the patient to appreciate because of the rebound insomnia that occurs during the withdrawal period. As noted previously in this chapter, the natural assumption during the withdrawal from medication is, "This is how I will sleep without medications from now on." In combination with a careful weaning process, sleep diaries may serve as the "hard data" to demonstrate to the patient that this assumption is not true.

THE EFFICACY OF CBT

There are a variety of studies that attest to the efficacy of behavioral treatments for primary insomnia. These studies have been reviewed in two meta-analyses *(51,52)*. Results from the two quantitative reviews are as follows: 32–41% global improvement in sleep following behavioral treatment where SL was reduced by 39.5–43% (effect sizes: 0.87–0.88), number of intermittent awakenings was reduced by 30–73% (effect sizes: 0.53–0.63), duration of intermittent awakenings was reduced by 46% (effect size: 0.65) and TST increased by 8–9.4% (effect size: 0.42). In actual minutes, pre–post measures revealed that patients fell asleep 24–28 minutes sooner, had 0.5–1.2 fewer awakenings and obtained about 30–32 more minutes of sleep a night. Comparative data showed that SRT or SCT yielded the greatest improvement, followed by multicomponent therapies. Treatment gains were maintained or enhanced over follow-up periods ranging from 3 weeks to 3 years. In addition to these data, there is a study by Morin and colleagues that suggests that behavior therapy yields, during acute treatment, comparable results to pharmacotherapy for insomnia and that behavior therapy has better long-term efficacy *(51)*. A recent study by our group *(53)* confirms this finding in a comparative meta-analytic study and extends it by demonstrating that during acute treatment behavior, therapy yields results comparable to those of pharmacotherapy and may provide superior results for sleep-onset problems.

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14

Pharmacological Treatment of Insomnia

Hrayr P. Attarian

INTRODUCTION

Insomnia is the most common sleep-related complaint and the second most common overall complaint (after pain) reported in primary care settings. It affects 35% of the general population, according to the 1984 report of the National Institutes of Mental Health *(1)*. Insomnia is not defined by total sleep time but by the inability to obtain sleep of sufficient length or quality to produce refreshment the following morning. For example, a person who needs only 4 hours of sleep does not have insomnia if he or she is refreshed in the morning after having 4 hours of sleep, whereas someone who needs 10 hours of sleep may have insomnia if he or she does not feel refreshed even after 8 hours of sleep. Contrary to popular lore, psychiatric or psychological factors are not the most frequent causes of insomnia. Insomnias can be divided into two major categories: the primary insomnias and the secondary insomnias. As discussed elsewhere in this volume, primary insomnias are conditions in which the insomnia is the main pathophysiological process, whereas secondary insomnias are conditions where the insomnia is a symptom of another disorder.

Primary Insomnias

Briefly, the primary insomnias are as follows:

1. Psychophysiological insomnia: a disorder of somatized tension and learned sleep-preventing associations that results in a complaint of insomnia and associated decreased functioning during wakefulness.
2. Idiopathic, or childhood-onset, insomnia: a lifelong inability to obtain adequate sleep that is presumably due to an abnormality in the neurological control of the sleep–wake system.
3. Sleep state misperception insomnia: complaints of insomnia occur without any objective evidence.

The treatment of most primary insomnias is a combination of behavioral and pharmacological therapies.

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Secondary Insomnias

Restless legs syndrome (RLS) is a common condition found in varying degrees in up to 10% of the population. The four cardinal symptoms are as follow:

1. A desire to move the legs.
2. Accompanying paresthesias that are characterized as uncomfortable or indescribable.
3. Motor restlessness.
4. Worsening of symptoms at night and at rest.

Symptoms of RLS may worsen with administration of tricyclic antidepressants or selective serotonin reuptake inhibitors and during pregnancy.

Menopause-related insomnia is a high level of sleep disturbance occurring in about 42% of middle-aged women. Other secondary insomnias include insomnia due to other sleep disorders, insomnia due to poor sleep hygiene, neurological, psychiatric, other sleep disoders or other medical conditions, and medication-induced insomnia. Secondary insomnias most often respond to the treatment of the underlying cause. In this chapter, only the pharmacological treatments of primary insomnias, menopause-related insomnia, and RLS are discussed.

HISTORICAL PERSPECTIVES

In the late 1800s, two compounds similar to alcohol were used to treat insomnia: paraldehyde and chloral hydrate. Synthesized by Justin Liebig in 1832, chloral hydrate is the oldest synthetic hypnotic agent. It has been used since 1869 as a hypnotic. It is still used for this purpose, but only rarely *(2)*. These two medications fell out of favor because of adverse effect profiles and problems with withdrawal after the advent of barbiturates in the early 20th century. Barbiturates were widely used as treatments of choice for insomnia for about half a century. In the 1950s, problems with tolerance, addiction, withdrawal, and overdose became apparent. Meprobamate was introduced to solve these issues, but it and its congeners turned out to have the same problems of addiction, tolerance, and withdrawal as the barbiturates. In 1960, chlordiazepoxide was introduced as the first benzodiazepine. Since then, the safety and efficacy of this class has made the former methods of pharmacological treatment of insomnia obsolete. There is much controversy regarding the incidence of addiction, tolerance, and dependence with benzodiazepine use. Because of this, many natural products have been studied as insomnia drugs. In 1970 L-tryptophan, an amino acid precursor of serotonin, was found to be effective in the treatment of insomnia *(3)*. In 1989, cases of eosinophilia-myalgia syndrome from all over the world were being reported in association with manufactured L-tryptophan *(4–6)*. In November 1989, the substance was recalled. By July 1990, only in the United States, 1531 cases were reported, with 27 resulting in death despite treatment and discontinuation of the drug *(5)*. By the early 1990s, L-tryptophan became obsolete as a hypnotic.

Current Pharmacological Therapies for Insomnia

A large proportion of people with persistent insomnia are not treated medically for their insomnia. Of patients suffering from insomnia, 25–30% self-medicate with either alcohol, over-the-counter (OTC) hypnotics, or a combination of the two *(7)*. Among people with insomnia, alcohol is the most commonly used substance for self-medicating.

Antihistamine OTC Hypnotic Drugs

Among the pharmaceutical substances, the OTC antihistamine hypnotics are the most used by insomnia sufferers and the most recommended and prescribed by physicians despite absence of data supporting their efficacy and the presence of several studies showing significant adverse effects. In 2000, Weiler and colleagues *(8)* looked at the effects of fexofenadine (an antihistamine), diphenhydramine, and alcohol on a person's ability to drive. They enrolled 40 licensed drivers with seasonal allergic rhinitis who were 25 to 44 years of age. The drivers were randomized to receive either placebo, fexofenadine (60 mg), diphenhydramine (50 mg), or alcohol (approximately 0.1% blood alcohol concentration). Their driving abilities were tested on the Iowa Driving Simulator. Participants had similar performance when treated with fexofenadine or placebo. After alcohol use, overall driving performance was poorer. After participants took diphenhydramine, driving performance was poorest, indicating that diphenhydramine had a greater impact on driving than did alcohol *(8)*. In 2003, Basu et al. published their data examining hypnotic use in a group of 1627 individuals age 65 and older over a period of 12 years. They found that prescription sedative/hypnotic use remained relatively stable, whereas OTC sedative use, principally diphenhydramine, increased substantially. They also found a positive association of this drug with cognitive impairment in older adults without dementia *(9)*.

Other researchers also have published reports discouraging the use of antihistamines as sedative/hypnotics because of their poor side-effect profile, propensity for drug–drug interactions, and lack of proven efficacy *(10,11)*.

In conclusion, OTC hypnotics containing antihistamines should be avoided in the treatment of insomnia because of their lack of clinically proven efficacy and significant adverse effect profile.

Herbal and Dietary Supplements Used as Hypnotics

Also available over the counter are herbal and dietary supplements. Two of these—melatonin and valerian root—are marketed as sleep aids.

Several studies have shown efficacy of melatonin in the treatment of circadian rhythm problems. As far as its use in primary insomnia, there is some evidence that melatonin may be helpful in the treatment of age-related insomnia. Zhadonova et al. conducted a double-blind, placebo-controlled study comparing 15 subjects over

50 years of age who slept normally to another group of subjects who exhibited actigraphically confirmed decreases in sleep efficiency *(12)*. All 30 received, in randomized order, a placebo and three melatonin doses (0.1, 0.3, and 3 mg) orally 30 minutes before bedtime for 1 week. Treatments were separated by 1-week washout periods. Sleep data were obtained by polysomnography on the last 3 nights of each treatment period. The data demonstrated that the physiological melatonin dose of 0.3 mg restored sleep efficiency, acting principally in the mid third of the night; it also elevated plasma melatonin levels to normal. The pharmacologic dose (3 mg), like the lowest dose (0.1 mg), also improved sleep; however, it induced hypothermia and caused plasma melatonin to remain elevated into the daylight hours. Although control subjects, like insomniacs, had low melatonin levels, their sleep was unaffected by any melatonin dose *(12)*. Melatonin has also been shown to help aleviate chronic sleep-onset insomnia in children. Smits et al., in the Netherlands, studied 40 elementary school children, 6 to 12 years of age, who suffered from chronic sleep-onset insomnia for more than 1 year *(13)*. The study was double-blind and placebo-controlled. The children were randomly assigned to receive either 5 mg of melatonin or placebo. The study consisted of a 1-week baseline, followed by a 4-week treatment period. The study demonstrated that 5 mg of melatonin taken at 6 PM was relatively safe in the short term and significantly more effective than placebo in advancing sleep onset and increasing sleep duration in school children with chronic sleep-onset insomnia *(13)*. Another group in whom melatonin seems to help alleviate insomnia are people with schizophrenia. Shamir et al. enrolled 19 subjects who met the *DSM–IV* criteria for schizophrenia, in a double-blind, randomized, cross-over, clinically based trial. They were given either 2 mg of controlled release melatonin or placebo for two treatment periods of 3 weeks each with 1-week washouts between treatment periods. Those patients who had poor sleep at baseline had significant improvement in sleep efficiency with the melatonin (80%) compared to when they were on placebo (67%). They also had a significant increase in sleep duration (on average by 45 minutes) and also a significant reduction in sleep latency (SL) on the average (by 40 minutes) *(14)*. The data available, however, do not support its use as a wide-spectrum hypnotic. Additionally, there is little information on its long-term safety *(15,16)*. The reason it seems to improve sleep in the above mentioned distinct population groups is most likely based on the fact that they all had low endogenous melatonin, which most primary insomniacs do not *(12,14,17)*. This is the same theory by which melatonin is thought to work in circadian rhythm problems. In fact, Stone et al. studied its effects in healthy volunteers. They compared melatonin given at 11:30 PM and at 8 PM to temazepam given at similar times. They measured both sleep parameters and core body temperature. They concluded that melatonin given at 11:30 had no significant clinical effect on nocturnal sleep in healthy individuals. Hypnotic activity of melatonin, when given in the early evening (presumably in the absence of endogenous melatonin), was similar to 20 mg of temazepam *(18)*.

Over the past few years, multiple small trials, both open-label and double-blind (placebo-controlled and using oxazepam as an active control) have shown clinically significant polygraphic and subjective improvement in the sleep of patients with primary insomnia who were given different valerian products at doses ranging from 460 to 600 mg. Dominguez et al. gave 470 mg of valerian root to 23 volunteers with complaints of persistent insomnia for 2 weeks. Twenty subjects followed through with the study. Of the 20 volunteers, 16 rated their sleep as moderate at the end of the first week. Fifteen of those rated their sleep as extremely improved at the end of the second week. No significant side effects were reported *(19)*. The same year (2000), Donath et al. enrolled 16 adult patients with psychophysiological insomnia in a double-blind, placebo-controlled trial of valerian extract. They used both objective (polysomnographic) measures and subjective questionnaires. Their study duration was also 2 weeks. They showed statistically significant improvement in both subjective and objective sleep parameters such as reduced SL, increased sleep efficiency, and increased slow wave sleep with valerian root that was more pronounced with continued use. Again, no serious adverse effects were reported *(20)*. Fussell et al. reported similar results in an open label trial of 250 mg of valerian with 60 mg of hop extract *(21)*. Dorn, comparing valerian to oxazepam as an active control, randomized 75 subjects with primary insomnia to either 10 mg of oxazepam or 600 mg of valerian. The outcome measures were standardized questionnaires assessing subjective improvement of sleep. In both groups, sleep quality improved significantly but no statistically significant difference could be found between groups. Again, no serious adverse effects were reported *(22)*. In 2002, Ziegler et al. replicated the results of Dorn in a larger group of subjects (202) with primary insomnia showing again comparable efficacy of 600 mg of valerian to 10 mg of oxazepam during a 6-week treatment phase *(23)*. Valerian has also been shown to improve sleep after benzodiazepine withdrawal. Poyares and colleagues studied 19 insomniacs who had been on nightly benzodiazepines for an average duration of 7.1 years. The subjects were withdrawn from benzodiazepines and were randomized to either placebo or valerian. The valerian group showed significant subjective improvement in sleep and decreased wake after sleep onset time (WASO) vs the placebo group *(23)*. There are other preliminary studies looking at other herbal supplements such as essential oil of Citrus aurantium L. (sour orange) *(24)* and other concoctions that have varying ingredients of herbal products *(25)*. These studies, however, did not produce any conclusive evidence of clinically significant efficacy of these substances.

In conclusion, among the herbal supplements, valerian shows promise as an effective hypnotic with little adverse effects. Melatonin seems effective only in certain special circumstances discussed above. No other herbal supplement has been studied well enough to suggest its efficacy as a hypnotic. Additionally, all herbal supplements discussed previously lack long-term safety data and there are no Food and Drug Adminstraiton-regulated standard formulations of valerian, melatonin, or any other herbal supplements.

Antidepressants

Because of concerns of benzodiazepine tolerance, addiction, and dependence, antidepressants (specifically amitriptyline and trazodone) have been used more frequently in the treatment of insomnia. There has been an upward trend in the number of antidepressants that were prescribed for insomnia since 1987, despite the paucity of reliable data regarding their efficacy as hypnotics and the presence of lingering daytime sedation after nighttime administration and other adverse effects that are discussed here *(26)*. Drs. Walsh and Schweitzer obtained data from the National Disease and Therapeutic Index , which samples office-based physicians in 24 specialties. They looked at total drug mentions for the treatment of insomnia from 1987 to 1996. Total drug use for the treatment of insomnia fell 24.4%. Hypnotic use decreased 53.7%, and antidepressants increased 146%. This demonstrates a dramatic shift to use of antidepressants in lieu of hypnotics for the symptomatic treatment of insomnia *(26)*. In fact, trimipramine and trazodone are the only two antidepressants with some clinical data regarding efficacy in insomnia. Scharf and Sachais administered 150–400 mg of trazodone to six depressed patients with significant sleep disturbances in an 8-week single-blind study design. Patients were evaluated by psychological questionnaires and polysomnography. Five of the six subjects completed treatment. There was statistically significant improvement in SL (by 44%), total sleep time (14%), stage 4 sleep (an increase of 153%), and sleep efficiency (by 80.6%) after 5 weeks of treatment *(27)*. There have been other reports of its efficacy as a hypnotic in the literature *(28–30)*.

Of note, all these trials were small and the subjects enrolled in them did not have primary insomnia but insomnia and comorbid depression. Trazodone has significant lingering daytime sedation even at low doses *(31)* and can cause significant rebound insomnia *(32)*. Incidentally, when Montgomery et al. tried trazodone in a small group of insomniacs, in addition to rebound insomnia they reported a discrepancy between subjective and objective improvement of sleep. These subjects all reported subjective improvement but had absolutely no change in their SL and duration polysomnographically *(32)*. Unlike other antidepressants, trazodone does not tend to aggravate RLS and periodic limb movements (PLMs). Recently, Riemann et al. studied trimipramine in primary insomnia. They enrolled 55 subjects in a double-blind, placebo- and benzodiazepine-controlled study. Trimipramine was used at an average dose of 100 mg over a period of 4 weeks. Trimipramine improves subjective sleep and objective sleep efficiency but not sleep duration. There was no evidence of any rebound effect from trimipramine. Side effects from trimipramine were only marginal *(33)*. In conclusion, antidepressants have the adverse effects of lingering daytime sedation after nighttime administration and other adverse effects (with tricyclics aggravation of RLS and anticholinergic effects) makes them poor choices for the treatment of insomnia.

Benzodiazepines

The benzodiazepines are γ-aminobutyric acid (GABA) agonists. They potentiate the action of GABA by displacing an endogenous inhibitor of GABA receptor bind-

Table 1
Benzodiazepines Approved in the United States for the Treatment of Insomnia

Drug	T 1/2 half life	Peak plasma level	Active metabolites	Type
Quazepam	39 hours	2 hours	Yes	Long half-life
Estazolam	10–15 hours	0.5–2 hours	No	Medium half-life
Flurazepam	48–120 hours	2 hours	Yes	Long half-life
Temazepam	8–15 hours	30–60 min	No	Medium half-life
Triazolam	1.5–5.5 hours	15–30 min	No	Short half-life

ing. They have potent hypnotic, muscle relaxant, anticonvulsant, and anti-anxiety properties.

Benzodiazepines act nonselectively at two central receptor sites, named omega(1) and omega(2), which are located in different areas of the central nervous system. The sedative action of benzodiazepines is related to omega(1) receptors, whereas omega(2) receptors are responsible for their effects on memory and cognitive functioning *(34)*. According to their pharmacokinetic profile, benzodiazepines can be classified into three groups: short half-life (<3 hours), medium half-life (8–24 hours), and long half-life (>24 hours). Table 1 lists those benzodiazepines approved for the treatment of insomnia.

Benzodiazepines are proven to be efficacious in the treatment of insomnia. In 2000, in Canada, Holbrook et al. *(35)* published a meta-analysis of benzodiazepine trials in primary insomnia. They identified 89 randomized controlled trials but excluded 44 from the meta-analysis for various reasons. The remaining 45 randomized controlled trials represented 2672 patients. Twenty-seven studies compared a benzodiazepine with a placebo, 13 compared a benzodiazepine with an alternate active treatment, and 5 studies involved a combination of both. The duration of the studies ranged from 1 day to 6 weeks. There was a statistically significant difference of SL and sleep duration both subjectively and objectively between a benzodiazepine and placebo. The question of whether tolerance to any sleep-promoting effect of benzodiazepines occurs could not be answered because all of the trials eligible for the meta-analyses were of short duration. Although more adverse effects were experienced by patients taking a benzodiazepine for the treatment of insomnia, dropout rates in the benzodiazepine and placebo groups were similar *(35)*.

Most benzodiazepine adverse reactions are viewed as extensions of the therapeutic effect beyond the desired time. Mendelson et al. looked at the reported rate of adverse effects in a 1000-bed hospital over a period of 3 years and discovered that the median frequency of reported adverse reactions was 0.01%, or 1 in 10,000 doses. The vast majority of reactions was considered mild, and without sequelae. All adverse reactions occurred in patients over 55 years old except for four patients under age 50 who received lorazepam *(36)*. Temazepam, the most commonly used benzodiazepine as a hypnotic, has been shown to be safe even in the elderly *(37)*.

The use of benzodiazepines has been generally restricted in the treatment of insomnia because of concerns of addiction, dependence, and tolerance. The risk of habituation and abuse, however, is lower than previously thought in patients who are properly diagnosed and use these medications for medicinal purposes *(38)*. In a double-blind fashion, Roehrs et al. gave 18 subjects with insomnia 1 week of triazolam and 1 week of placebo. The number of triazolam capsules taken nightly was stable and the number of placebo capsules variable. It was concluded that insomniacs showed no short-term escalation of triazolam dose, but did choose an increased and variable number of placebos, a pattern that was interpreted as being insomnia relief-seeking behavior *(39)*. Schenck and Mahowald followed 170 patients for 12 years who were receiving nightly benzodiazepines for the treatment of a variety of sleep disorders including injurious sleepwalking and sleep terrors (n = 69); rapid eye movement sleep behavior disorder (n = 52); chronic, severe insomnia (n = 25); and RLS/periodic limb movement disorder (n = 24). Only 2% had relapses of alcohol or chemical abuse requiring hospitalization and another 2% at times misused their medications *(40)*.

In conclusion, benzodiazepines are effective and safe in treating primary insomnia. There some strong data to suggest that in the absence of prior history of alcohol or substance abuse, when used judiciously, that the risk of tolerance, abuse, dependence and addiction is low. More studies are needed to fully answer that question, however.

Imidazopyridines

The newer non-benzodiazepine agents (*see* Table 2) zopiclone, zolpidem, and zaleplon, have a hypnotic action comparable with that of benzodiazepines, but they display specific pharmacokinetic and pharmacodynamic properties. They are structurally unrelated to benzodiazepines and belong to a new chemical class, the imidazopyridines. These three agents all share a short plasma half-life and limited duration of action. Additionally, these agents are selective compounds that interact preferentially with omega(1) receptors (sedative effect), whereas benzodiazepines also interact with omega(2) receptors (adverse effects on cognitive performance and memory). Zaleplon is characterized by an ultrashort half-life, zolpidem and zopiclone have longer half-lives. These properties, together with the low risk of residual effect, may explain the limited negative influences of these agents on daytime performance. Cognitive functions are better preserved by non-benzodiazepine agents than by benzodiazepines *(34)*. When present, cognitive deficits almost always coincide with the peak plasma concentration, especially in the first hours after drug administration, whereas cognitive testing administered 7–8 hours later (i.e., in the morning) generally shows no impairment *(34)*.

Zolpidem is an effective and safe hypnotic with minimal adverse effects and no dependence, withdrawal, tolerance, or rebound insomnia over long-term use. Zolpidem's elimination half-life is 2.2 hours, and peak plasma levels are reached in 90 minutes. The dose needs to be adjusted in the setting of hepatic impairment but

Table 2
Nonbenzodiazepine Hypnotics

Drug	T 1/2 half life	Onset of action	Peak plasma conc	Active metabolites
Zolpidem	1.5–2.4 hours	30 minutes	1.5 hours	No
Zaleplon	1 hours	30 minutes	1 hour	No
Zopiclone	5–6 hours	30 minutes	2 hours	No

not with altered renal function. Schlich et al. as early as 1991, studied 107 patients with insomnia, about 60% of whom were over 60 years of age. The subjects were given 10 mg of zolpidem on a nightly basis for 6 months. An improvement in all efficacy parameters—time taken to fall asleep, total amount of nocturnal sleep, and number of nocturnal awakenings—was reported by the investigator and the patients; the improvement was evident from the first evaluation day and was maintained throughout the trial. Improvement was also maintained during the washout period with a lack of rebound insomnia. There was no sign of withdrawal symptoms and tolerance to zolpidem did not develop over the 6-month treatment period. Adverse events were mild and infrequent, and tended to resolve with a dose reduction *(41)*. The following year, Maarek and colleagues reported the results of their open-label zolpidem trial. They enrolled 96 subjects who received 10–20 mg of zolpidem a night for 6 to 12 months. Again, improvement in all sleep parameters was noted in 90% of subjects with no rebound and withdrawal effects on discontinuation *(42)*. Saletu-Zyhlarz et al., in a single-blind, placebo-controlled crossover study, compared 10 mg of zolpidem to placebo. Fifteen adult patients diagnosed with nonorganic insomnia were enrolled. Objective and subjective sleep and awakening quality measures were investigated in 3 subsequent nights in the sleep laboratory. There was a significant lengthening of the total sleep period and total sleep time, an improvement in sleep efficiency and a shortening of SLs after zolpidem as compared with placebo. Zolpidem also increased the length of stage 4 and stage 3 + 4 non-REM sleep as compared with placebo *(43)*.These are some of the important studies looking at zolpidem; there are others in the medical literature that have produced results, concordant with the above.

Zaleplon also is an effective and safe hypnotic *(44)*. The onset of action is approximately 30 minutes, and the duration of action is about 4 hours. Peak zaleplon serum concentrations occur in about 1 hour, and its elimination half-life is also about 1 hour. Similar to zolpidem, its dose needs to be adjusted with altered hepatic function but not with renal impairment. The Zaleplon Clinical Study Group looked at the efficacy and safety of three doses of zaleplon, a novel compared with those of placebo in outpatients with insomnia in this 4-week study, using 10 mg of zolpidem as active control. Post-sleep questionnaires were used to determine treatment effects on the patient's perception of sleep, development of tolerance during therapy, or rebound insomnia or withdrawal on discontinuation of therapy. SL was significantly shorter throughout the 4 weeks of study with any dose of zaleplon compared

to placebo. Zaleplon also had significant effects on sleep duration, number of awakenings, and sleep quality compared to placebo. No pharmacological tolerance developed with zaleplon and there were no indications of rebound insomnia or withdrawal symptoms after treatment discontinuation. There was no significant difference in the frequency of adverse events with active treatment compared to placebo. These results show that zaleplon provides effective treatment of insomnia with a favorable safety profile *(45)*. A similar study was done to look at its efficacy and safety in the elderly (>65 years) population. Again, zaleplon proved to be a safe and effective treatment for insomnia in the elderly with no significant adverse effects of rebound insomnia *(46)*. Because of its short half-life, there is no residual sedation when zaleplon is administered in the middle of the night; hence, it is the ideal medication for sleep maintenance insomnia. Walsh et al. assessed residual sedation after 10 mg of zaleplon in a randomized, double-blind, placebo- and active drug-controlled cross-over study with 30 mg of flurazepam (as an active control). The drug (zaleplon, flurazepam, or placebo) was taken during a nocturnal awakening in patients with sleep maintenance insomnia. Twenty-two healthy sleep maintenance insomniacs were enrolled and received zaleplon, flurazepam, or placebo after an experimental awakening 3.5 hours after bedtime on 2 consecutive nights. Residual sedation was measured with SL testing (5 and 6.5 hour postdrug), and other psychometric tests. Zaleplon did not differ from placebo on any measure of residual sedation; flurazepam showed significant sedation on all measures *(47)*.

A related medication, zopiclone (not available in the United States), has also been shown in several studies to be as effective as benzodiazepines in relieving symptoms of insomnia and as safe as the other "Z" medications *(35)*. It can also be helpful in shift-work insomnia. In a recent study, 29 shift workers suffering from insomnia were included and treated with zopiclone (7.5 mg/day) or placebo according to a random, double-blind protocol. Patients completed a sleep diary and a wrist actigraph was used to evaluate episodes of rest and activity. A self-administered subjective sleep questionnaire was filled out just after awakening. Zopicone was found to increase the duration of sleep significantly over the baseline duration after the first and second night on duty. Subjective estimation of sleep was better in patients taking zopiclone who exhibited a smaller number of shorter awakening episodes *(48)*.

Another method of use of hypnotics have come into favor in recent years that maximizes benefits for chronic insomniacs and minimizes tolerance or dependence. Several studies, mainly with zolpidem, have shown that non-nightly, discontinuous use with stimulus control therapy (SCT) has shown to be both effective and safe in chronic use *(49)*. In 2002, Hajak et al. published their data on discontinuous, non-nightly hypnotic therapy in the treatment of chronic insomnia. In a prospective, observational open study in 550 primary care settings throughout Germany, 2690 patients with chronic insomnia were treated with zolpidem according to an "as-needed" administration treatment schedule (up to five tablets per week chosen by the patient), in addition to the optional use of SCT, during drug-free nights. After

the 3 weeks of treatment, in 63% of patients the weekly number of tablets used was reduced in contrast to baseline without any significant impact on the treatment efficacy. Efficacy of treatment was rated as very good or good in 93% by the investigators. Adverse events were observed only in 1.2% of patients and were generally of mild nature. No serious adverse event occurred *(49)*.

In conclusion, the non-benzodiazepine hypnotics (zolpidem, zoplicone, and zaleplon) are safe and effective hypnotics with minimal adverse effects and no dependence, withdrawal, tolerance, or rebound insomnia over long-term use *(43,45,46,50)* Of course given the relatively small number of studies further research is warranted to assess both the efficacy and the safety of long-term use.

SECONDARY INSOMNIAS REQUIRING SPECIFIC PHARMACOLOGICAL TREATMENTS

Restless Legs Syndrome

RLS and the resulting insomnia respond only to medication. Behavioral therapies have no role in the treatment of RLS. Sometimes, antidepressants and other medications aggravate RLS. Cessation of these medications helps alleviate the symptoms. In those patients who have low serum ferritin, iron replacement, may be helpful. Most patients, however, require medication. The most effective medications for treating RLS symptoms belong to three distinct classes: (1) the dopaminergics agents, e.g., pramipexole *(51,52)*, ropinirole hydrochloride *(53,54)*, pergolide mesylate *(55)* bromocriptine mesylate *(55)*, and levodopa *(56)*; (2) the opiates *(57)*; and (3) the benzodiazepines, especially clonazepam *(58)*. Studies have shown that the newer anticonvulsants gabapentin *(59,60)* and clonidine (especially in patients who do not have a large amount of PLMs) *(61)* are also effective in controlling RLS. The doses of the above medication used in the treatment of RLS are usually much lower than the doses utilized in the treatment of other conditions such as Parkinson's disease, pain, anxiety, seizures, and other medical conditions for which the above medications are effective. In rare instances, higher doses are reached by titrating to the patients' symptoms.

Menopause-Related Insomnia

In menopause-related insomnia, estrogen replacement therapy (ERT) may control insomnia along with other menopause-related symptoms *(62,63)*. The recent medical problems reported with ERT have led to a search for other alternatives. One herbal alternative, Black Cohosh, has been studied but there is no conclusive evidence as to its efficacy in menopausal insomnia *(64)*.

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